3rd
Edition

Textbook of
NEPHROLOGY

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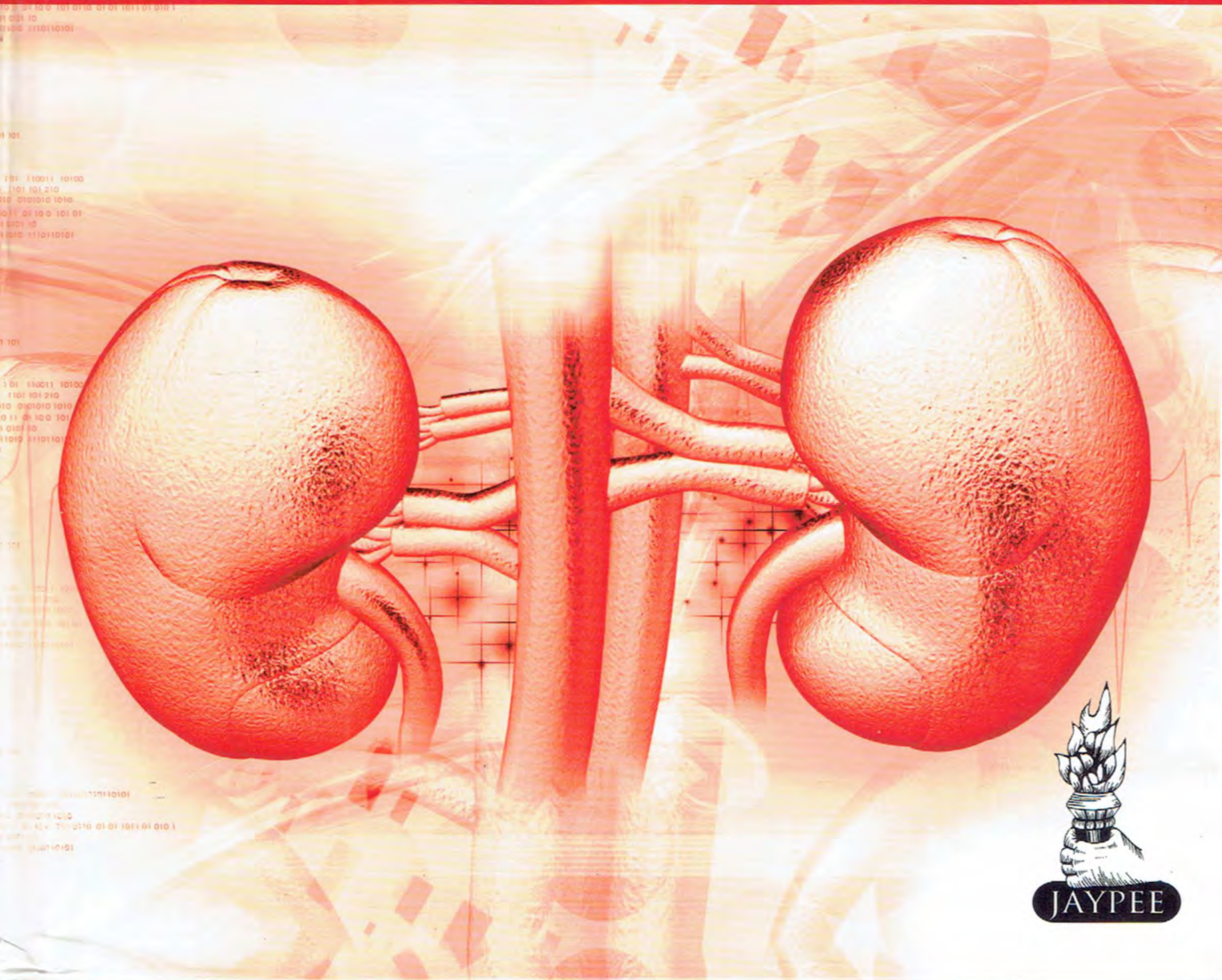

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Textbook of
NEPHROLOGY

Third Edition

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Dedicated to

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Foreword to the Third Edition

Nephrology has made great strides during the last decade and demand for renal services has grown considerably throughout the world. A book highlighting practical and clinical aspects of nephrology fills an important gap on the subject. The last edition of the book was very well received and there was an urgent demand for revision of the book. All the chapters have been extensively revised and some new chapters have been added. Four new chapters dealing with Diabetes and Kidney have been included. Professor Mandal has large practical experience in this area of nephrology and has highlighted his observations in these chapters. The book has been supplemented with figures, tables and graphs. This makes it more readable. Professor Anil K Mandal and his co-authors deserve appreciation for the hard work they have done in preparing this book. I am sure this will serve the specific purpose for which it has been written.

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Foreword to the First Edition

This textbook, written very largely by people from the Asian-Pacific area, many of whom are now working in other parts of the world, is likely to fill a particular need for Asian-Pacific physicians. The chapters contain practical information giving formulas to assist the physician in making judgements on things like electrolyte disturbances and other practical problems which arise in nephrological practice. The chapter on dialysis is a useful one written for physicians rather than nephrologists and explaining the techniques in simple and practical terms.

The Editor, Anil K Mandal, is a distinguished and energetic nephrologist and nephro-pathologist who has managed to persuade a number of very talented academics to participate in this new venture. This textbook written for a specific purpose for Asian-Pacific physicians promises to be both a popular and useful text.

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Preface to the Third Edition

Third edition is an update of the second edition with addition of several new chapters on diabetes: what does high glucose higher than normal levels (70–99 mg/dL or 3.8 to 5.5 mmol/L) do to body function?, diabetes and sexual dysfunction and a logical approach to management of diabetes with a goal to prevention of complications. Diabetes-associated renal disease may not be due to diabetes as written by Professor Jai Prakash from Varanasi, India. The reason being Type 2 diabetes is not a well-defined entity, due to lack of assessment by 2-hour postprandial glucose level or glucose tolerance test. Therefore, some of these patients with so-called Type 2 diabetes may not have diabetes.

Nevertheless, diabetes has constituted a big part of nephrology practice with the intention to reduce proteinuria hence reducing the risk of end-stage renal disease (ESRD) and dialysis therapy. This intention was not accomplished as more and more diabetes patients are entering into dialysis programs. In the editor's practice, diabetes patients do not enter into dialysis, because editor pays total attention to glycemic control and does not prescribe renin-angiotensin inhibitor drugs or discontinues these drugs for patients who were receiving them at the time of first office visit. Diabetes is a self-care disease. Well-motivated patients understand that diabetes is a serious disease and do their best to keep sugar under control so that they do not develop the horrible complications such as foot ulcer, gangrene and kidney failure. Professionals should do everything to prevent renal failure and resulting dialysis treatment. It is with those goals in mind that the new chapters were added. Diabetes is the most common cause of sexual dysfunction in men and women and a major cause of family turmoil. This is an uncultivated and uninformed area. Thus, with the addition of this chapter, the editor feels that professionals may be alerted to the importance of the discussion of sexual function with their diabetes patients.

The focus of the third edition is a conservative nephrology practice clear of dialysis and transplantation. However, the chapters on dialysis and transplantation are retained to help trainees and those practitioners who are more interested in those two areas than others. The chapters are written based on observations and application of methods of diagnosis and management plans which work well for the patients. Thus, this book is a practical one to appropriately tackle problems pertaining to renal disease, hypertension, and diabetes. This book is not evidence-based resulting from clinical trials which are not helpful when it comes to direct patient care. Style of the book is succinct and lucid and is free of commercial interest. Finally, the editors are pleased to express a deep appreciation to all of the authors for their contribution to the enrichment of this third edition.

Anil K Mandal

Preface to the First Edition

The purpose of developing a volume in nephrology entitled *Textbook of Nephrology for the Asian-Pacific Physicians* is neither a gesture to crowd the publishing market with another nephrology book nor an intention to compete with any of the existing volumes in the medical books market. The purposes of developing a volume of nephrology for the Asian-Pacific physicians are discrete and do not overlap with those of any of the existing nephrology textbooks.

These purposes are: *(1)* There is a wide margin of difference in the currency exchange between the Western world and the Asian-Pacific countries. This currency difference makes books published in the Western world less or non-affordable to most practicing physicians including nephrologists in the Asian-Pacific countries. *(2)* Except in Japan and Australia, there are very few trained nephrologists in the Asian-Pacific countries. For example, there are hardly 240 trained nephrologists for an 800 million population in India, giving a ratio of 0.3 nephrologist per million or barely 1 nephrologist for every 3 million. The international directory of nephrology indicates that a similar or a lower ratio of the nephrologists per million population exists in many of the Asian-Pacific countries. *(3)* The system of continuous medical education in nephrology is also rather tenuous in the Asian-Pacific countries. Therefore, the practicing physicians in these countries have few or no avenues to obtain information or seek assistance while dealing with their patients who have major renal problems. In addition, I have consistently observed that the non-nephrologist physicians become more apprehensive by the findings of acidosis, rising serum potassium and blood urea nitrogen than other laboratory abnormalities in their patients. These purposes were embedded in the mind of the editors for sometime, and thus this book was conceived.

I have a hope that this *Textbook of Nephrology* would become affordable to most of the physicians in the Asian-Pacific countries.

This book is not complete due to the lack of inclusion of some other topics in nephrology; nonetheless, this text has covered major areas of nephrology to facilitate nephrology care in the Asian-Pacific countries. In addition, rather than not having a volume at all, this initial edition, at best, may serve as a forum to address the issues and the needs so that the next edition can be developed in a more comprehensive fashion.

The encouragement, support and contributions made by my distinguished colleagues from the USA and the Asian-Pacific countries for the completion of this volume are immeasurable. My special gratitude goes to Dr H Verdain Barnes, Professor and Chair, Department of Medicine, Wright State University, for providing me with the facilities that are conducive for this type of tedious work. My special thanks go to Mrs Chris Wert, Senior Secretary, Department of Medicine, Wright State University, whose dedicated work has turned this volume into reality. I am also very thankful to all the secretaries of the word processing satellite of the Wright State University, Medical Sciences Division, Dayton, Ohio, for consistently working with me to complete this volume. I am thankful to my elder daughter, Aditi Mandal, for her time and effort in the editorial work. Finally, I am very appreciative of Shri Jitendar P Vij of Jaypee Brothers Medical Publishers, New Delhi, for his keen interest in publishing this nephrology volume.

AK Mandal
Anil K Agarwal

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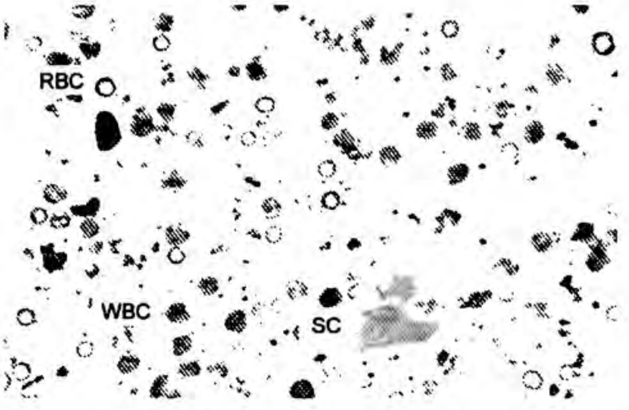


Figure 1: Cellular elements in urine. Red blood cells (RBCs) present as rounded cells without nucleus. White blood cells (WBCs) are slightly larger than the RBC and have granular appearance. Squamous cells (SCs) are large, irregular cells (*Chapter 1*)

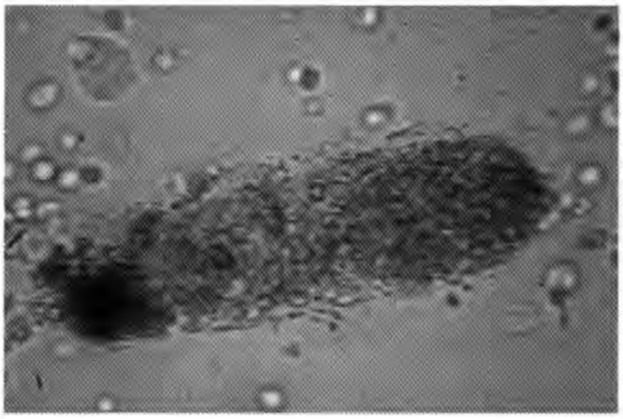


Figure 2: Red blood cell cast. Note numerous small RBCs packed within the cast, indicative of glomerular hematuria (*Chapter 1*)

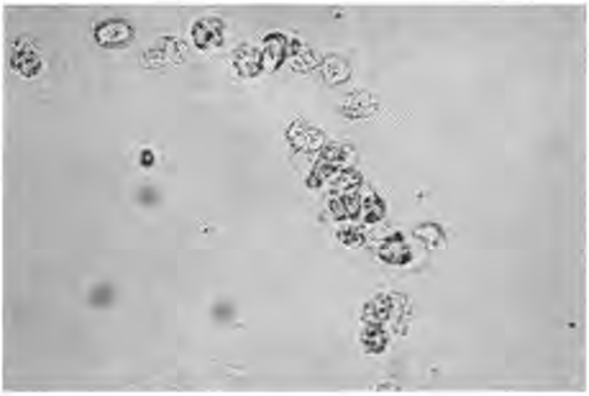


Figure 3: White blood cell casts. Note presence of multiple WBCs within the proteinaceous material in the shape of tubules (*Chapter 1*)

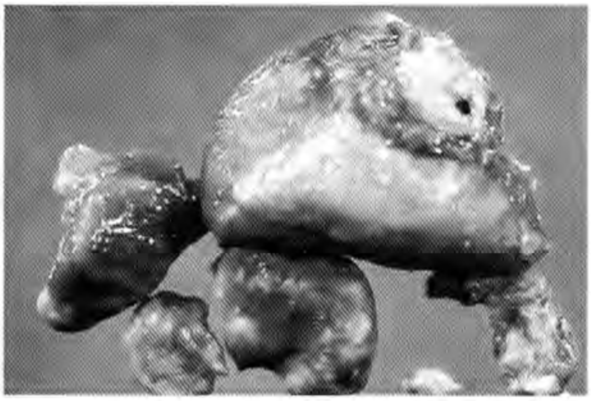


Figure 1: 35-year-old white female with classic distal RTA characterized by severe hypokalemia, persistent metabolic acidosis, and bilateral nephrolithiasis with recurrent passage of stones (*Chapter 5*)

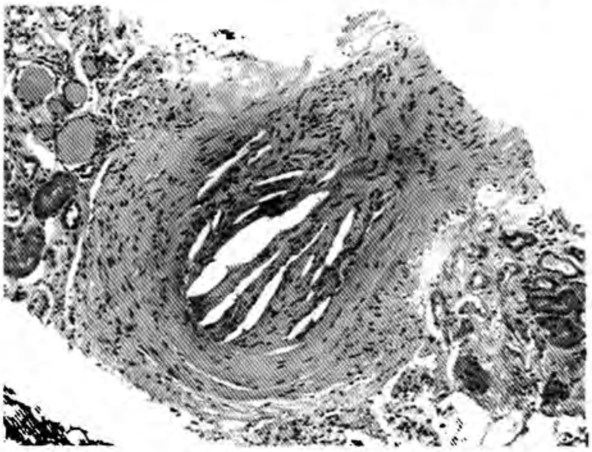
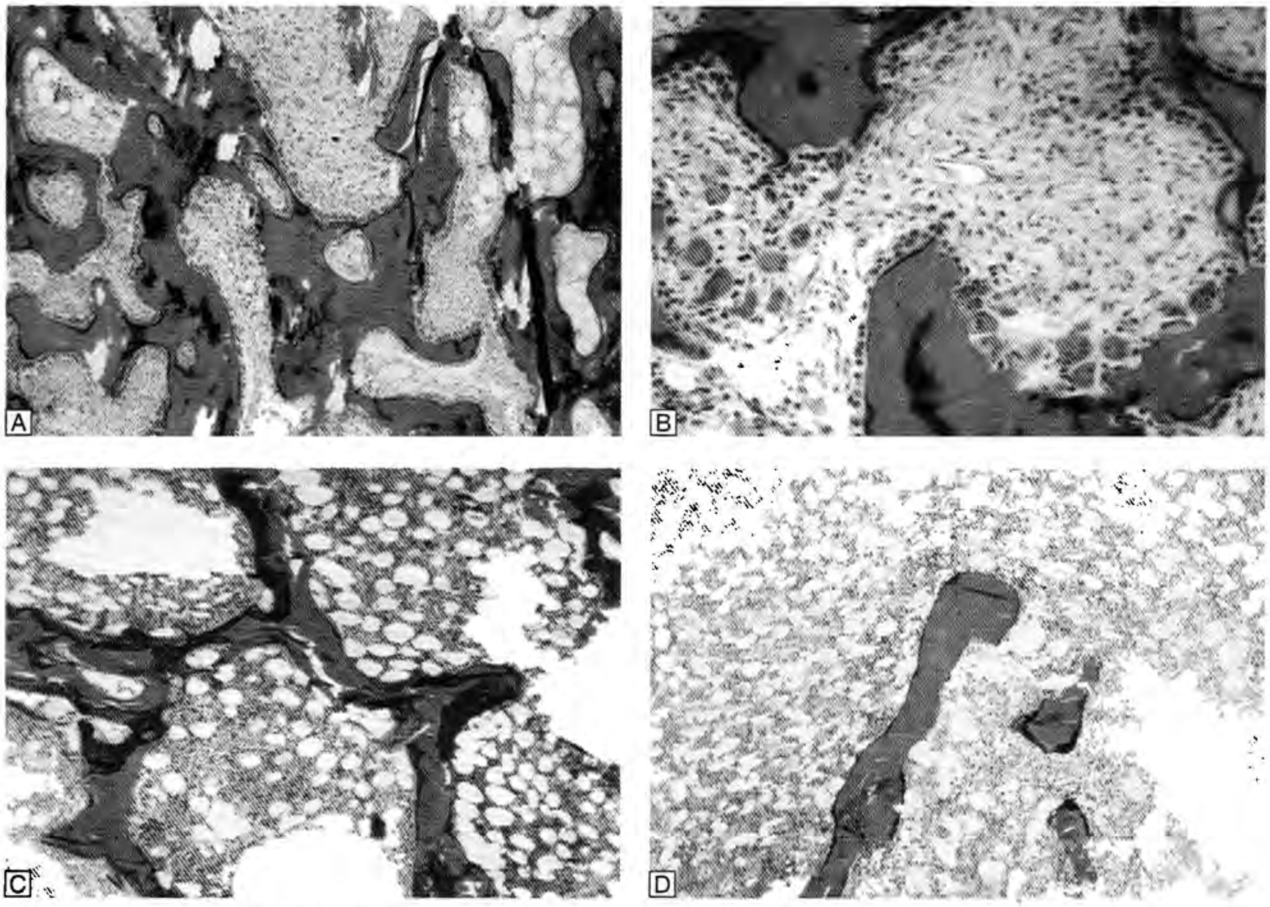


Figure 4: Histologic section of a needle biopsy of the kidney (Hematoxilin-Eosin stain) shows an arteriole with cholesterol embolization in organizing phase. The complete vascular occlusion is mostly by fibrotic tissue. Notice the intraluminal clefts that remain after the embolized cholesterol crystals dissolved during histologic processing. Earlier phases of the disease can demonstrate hystiocytic and giant cell reactions (*Chapter 29*)



Figures 4A to D: **Goldner-stained examples of bone histology. A. Osteitis Fibrosa** (low magnification) – large areas of consolidated bone marrow fibrosis, numerous osteoclasts (multinucleated giant cells) and several osteoid seams covered with osteoblasts (orange colored seam covered with a single layer of cells) are seen. In the top right corner, an area of normal bone marrow is present. **B. Osteitis Fibrosa** (high magnification) - multiple osteoclasts in a resorption cavity are seen in the lower right and an osteoid seam with osteoblasts is seen in the upper right. Bone marrow fibrosis is also present throughout. **C. Osteomalacia** (low magnification) – multiple, broad osteoid seams devoid of osteblasts are seen throughout and cover most of the bone surface. The bone marrow space is normal. **D. Adynamic Bone** (low magnification) – bone with thin osteoid seams but without osteoblasts is seen in the larger bone spicule on the left. In the two smaller bone spicules on the right, broad osteoid seams devoid of osteoblasts are suggestive of focal osteomalacia. The bone marrow space is normal (*Chapter 24*)

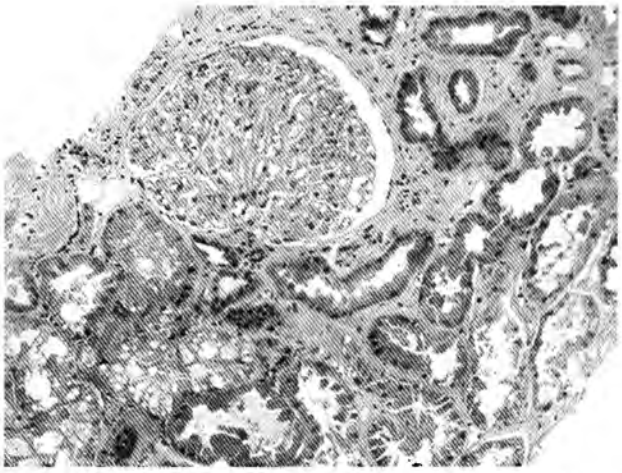


Figure 1: A hematoxylin and eosin-stained section reveals thickened glomerular capillary loops. There is focal mild interstitial fibrosis. (H&E, 20x objective) (*Chapter 31*)

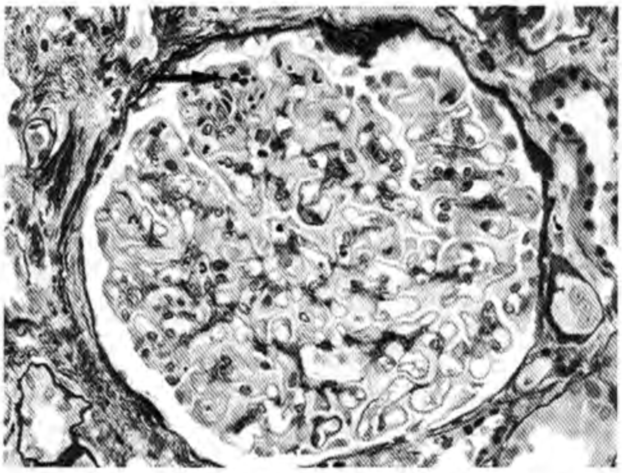


Figure 2: Glomeruli show segmental margination of leukocytes (arrow), a feature that is suggestive of renal vein thrombosis. Gomerular basement membrane "spikes" as seen on a silver stain are not well developed in this case. (Jones-methenamine silver, 60x objective) (*Chapter 31*)

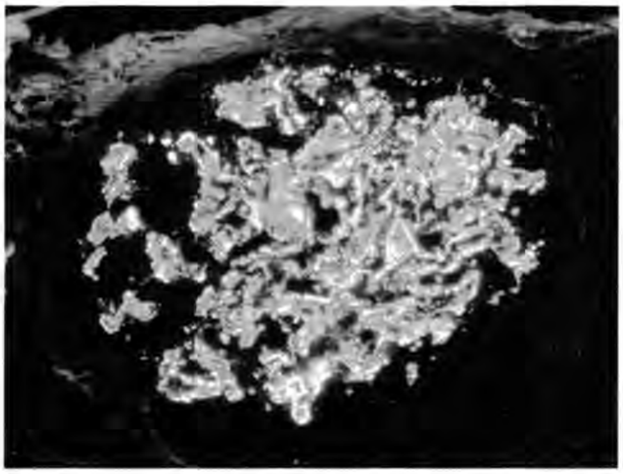


Figure 3: Glomeruli show global granular glomerular basement membrane staining for IgG. (Immunofluorescence, 40 x objective) (*Chapter 31*)

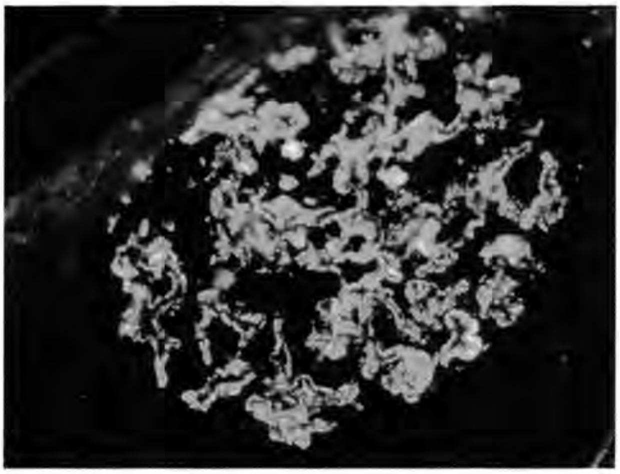


Figure 4: Glomeruli show global granular glomerular basement membrane staining for C3. (Immunofluorescence, 40x objective) (*Chapter 31*)

SECTION 1

FLUID, ELECTROLYTES, ACID-BASE DISORDERS AND CALCIUM-PHOSPHORUS METABOLISMS

- Evaluation of Patients with Kidney Disease
- Physiology of Urinary Concentration and Dilution and Diabetes Insipidus
- Hyponatremia: Etiology, Pathophysiology, and Management
- Hypernatremia: Pathophysiology, Diagnosis and Management
- Hypokalemia: Prevention and Treatment
- Hyperkalemia: Pathophysiology, Diagnosis, Treatment, and Prevention
- Metabolic Acidosis and Metabolic Alkalosis
- Metabolic Alkalosis: Pathophysiology and Management
- Polyuria and Diabetes Insipidus
- Calcium and Phosphorus Metabolism Associated with Clinical Disorders in Pediatric and Adult Population
- Generalized Edema (Anasarca): A Systematic Approach to Diagnosis and Management

1

Evaluation of Patients with Kidney Disease

Anil K Agarwal, Uday Nori

INTRODUCTION

In addition to the well-known excretory function, kidneys perform many other important metabolic and hormonal functions. They also play a vital role in regulating blood pressure. Thus, it is rather ironic that early stage kidney disease is often clinically silent. Even the biochemical abnormalities are subtle and symptoms curiously absent until late, when the dysfunction is rather advanced. For instance, even though proteinuria and hematuria signifying renal parenchymal damage may be present early on, symptoms of volume overload and uremia will only develop when the kidney damage is far advanced, often over extended period of time. Diagnosis of renal disease is frequently made incidentally when blood urea nitrogen (BUN) and serum creatinine (SCr) are found to be elevated on routine blood chemistry profile. If clinical symptoms or signs alone drive these or other diagnostic studies, most patients would be diagnosed with kidney disease in an advanced stage. Hence the cornerstone of the screening for kidney disease is identification of risk factors and risk stratification. Patients identified to have risk for developing kidney disease are examined in the clinic and tested in the laboratory periodically.

Since early kidney disease is asymptomatic, initial identification depends on laboratory parameters, such as elevated BUN and SCr, followed by the identification of the specific etiology by other diagnostic studies. This early diagnosis of kidney disease is critical in instituting disease specific treatment, reducing the progression of the chronic kidney disease (CKD), managing various complications of CKD (e.g., anemia, renal osteodystrophy), adjusting appropriate "renal dose" of various medications, avoiding nephrotoxins, and preparing for renal replacement therapy in timely fashion, if necessary.

Epidemiological studies over the past two decades have also identified several disconcerting phenomena that make screening for early stage CKD much more urgent. Many recent clinical trials identify that CKD is an independent risk factor for coronary artery disease and that the patients with CKD have a higher chance of dying with cardiovascular disease before reaching end stage renal disease (ESRD). Many national and international societies have now issued clinical practice guideline for large scale screening programs to identify patients with early CKD. It appears that renovascular disease and coronary vascular disease coexist.

These studies have also reported that the incidence and prevalence of CKD were vastly higher and rapidly increasing than previously thought. This "global epidemic" owes largely to the increasing burden of diabetes mellitus and hypertension. The economic impact of CKD and its treatment is enormous; as an example in United States alone it accounts for $25 billion annually.

The assessment of renal disease begins with estimation of glomerular filtration rate (GFR). Complete assessment of the patient with kidney disease can be accomplished by urinalysis, biochemical and immunological analyses, radiological tests and occasionally, a kidney biopsy. These tests are individualized to the specific renal condition of a given patient.

ASSESSMENT OF GFR

The best measure of renal function is GFR, which is defined as the sum of the ultrafiltrate produced by all the glomeruli per unit of time. GFR differs in people based on age, gender, race and nutritional state. However, it remains quite constant in a given individual in the absence of renal disease except for slow, age related decline. Thus, it is important to measure it periodically in those at risk of developing renal disease, as well as in those who already have CKD. To account for the GFR differences based on individual's weight, all GFR measurements are reported after normalization to 1.73 m^2 body surface area. This has allowed the novel staging system for the CKD based upon the level of GFR as introduced by National Kidney Foundation's 'kidney disease clinical practice guidelines' (Table 1). This staging system is now widely embraced internationally and includes a specific action plan of testing and treatment for each of the five stages.

There are various methods for measuring or estimating GFR. These are:

1. Direct measurement methods which are considered the gold standard because they are highly accurate, but are expensive and time consuming.
   a. Radionuclide scintigraphy: Intravenous injection of a known quantity of a radionuclide tracer (e.g., DTPA), which is filtered by kidneys but neither secreted nor reabsorbed, and the amount concentrated in the kidney is measured by a gamma camera. This method not only measures GFR accurately but also provides a split function in each kidney.
   b. Measuring renal clearance of extrinsic substances (e.g., inulin, iothalamate): Intravenous injection of a known quantity of an extrinsic substance that is freely filtered by the kidneys but neither secreted nor reabsorbed. Urine is then collected to measure the quantity of the substance excreted and the 'clearance' is calculated by the equation described below.
2. Measuring renal clearance of intrinsic substances (e.g., urea, creatinine) - A timed urine collection, typically 24-hour, for measuring the urea nitrogen or creatinine. The creatinine clearance (Ccl) (or urea clearance) is then derived from the clearance equation as below:

   Ccl (ml/min) = UV/P,

   Where,
   U = urine creatinine concentration (mg/deciliter),
   V = volume of urine (ml per minute, i.e., 24 hours volume/1440), and
   P = Serum creatinine (mg/dL).

   The average of urea and creatinine clearances is probably a more accurate method than either of the two alone. This is because of the compensation of the underestimation of GFR by the urea clearance by the overestimation of GFR by the Ccl.
3. Estimation equations that incorporate Scr, age, gender and race (MDRD-4, Cockroft-Gault equation) C-G equation: Ccl (ml/minute)= (140-Age in years) x Weight (in kg)/72 x Scr (For females, this value should be multiplied by 0.85)
4. Ccl can also be calculated by simply calculating reciprocal of Scr, i.e., Ccl = 1/Scr x 100
5. For routine longitudinal follow up in any individual patient, simple Scr and BUN are adequate since in any individual with stable health and standard diet, these remain constant. But these measurements are unreliable in accurately predicting GFR.

It must be emphasized that in any acute illness, most of the above methods are unreliable because of the rapidly changing GFR. A 24-hour urine Ccl is probably the closest estimate of the true renal function in this situation.

BUN is a protein metabolite that is cleared by the kidneys via glomerular filtration. BUN level is dependent upon rate of production, tubular reabsorption and secretion, making it an unreliable marker of renal function. For example, a misleadingly high level of BUN can occur in the absence of abnormal renal function

Table 1. Stages of chronic kidney disease

Stage	*GFR ml/ minute /1.73m²*	*Characteristics*
I	>90	Kidney damage with normal or increased GFR
II	60-89	Kidney damage with mild decrease in GFR
III	30-59	Moderate decrease in GFR
IV	15-29	Severe decrease in GFR
V	<15	Renal failure (ESRD if on dialysis)

if the production is increased (e.g., gastrointestinal bleeding, burns, steroid therapy, sepsis, etc.), or if the tubular reabsorption is high (e.g., intravascular volume depletion, poor cardiac output, etc.). A misleadingly low BUN level can be associated with advanced renal dysfunction in elderly, malnourished and bedridden patients, who do not have enough muscle mass (as in patients with cirrhosis).

SCr is the most commonly utilized measure of Ccl in day-to-day practice of medicine. Scr is also likely to be affected by many factors other than GFR, though to a lesser degree than BUN (Table 2).

Serial follow up of SCr, rather than the absolute value of creatinine, is more useful indicator of progression of renal function in a given patient, since the 'normal' creatinine could vary among individuals, in proportion of their muscle mass and diet. Thus, a low creatinine of 0.8 in an elderly, thin female may reflect advanced renal insufficiency, while a creatinine of 2.0 in a body builder may be associated with normal renal function.

In CKD, as the GFR declines, the tubular secretion of creatinine increases in a compensatory way, keeping the level of SCr unchanged. However, this compensatory mechanism gets saturated as GFR is reduced to 50 to 55 percent from baseline. At this point the SCr starts increasing gradually. Therefore, it can be surmised that a GFR change from 100 ml/min/m^2 to 60 ml/min/m^2 will not result in a change in the SCr. However, a change from 1.0 mg/dl to 1.2 mg/dl may signify that at least 50 percent GFR has been lost by that time, making it at least a stage 3 CKD.

Because of the compensatory tubular secretion of the creatinine, estimation of Ccl from spot SCr or total urine creatinine excretion in 24 hours usually overestimates GFR. Inhibition of tubular secretion of creatinine by cimetidine or trimethoprim can improve the accuracy of this estimation.

Table 2. Factors influencing level of serum creatinine

Elevation of Creatinine Value	*Decrease in Creatinine Value*
Excess protein intake, ingestion of creatine	Malnutrition
High muscle mass, vigorous exercise	Poor muscle mass, old age
States of catabolism, ketones, assay technique	Liver disease, assay technique
Male (high creatinine generation rate)	Female sex

The Cockcroft-Gault equation also modestly overestimates GFR. In children, Schwartz and Counahan-Barratt formulae are used similarly. A more accurate equation that applies to those with kidney disease is the Modification of Diet in Renal Disease (MDRD) equation, which calculates estimated GFR (eGFR). This is more difficult to calculate, but GFR calculators using this formula are widely available on various websites (e.g., www.kidney.org) and handheld devices. Even with this equation, concerns remain regarding its validity in diverse populations. It underestimates GFR in those without kidney disease.

Due to the fallacies of BUN and creatinine in estimating true GFR, and difficulty in measuring GFR by direct methods, there remains a need for a more accurate and easily available marker of kidney function to diagnose kidney disease early. Among several potential candidates, serum levels of cystatin C, a protein freely filtered and then metabolized by the tubules, is promising although still affected by factors other than GFR.

ASSESSMENT OF TUBULAR FUNCTION

The tubular function is responsible for dilution, concentration and acidification of urine.

This can be done by careful evaluation of osmolality, specific gravity, pH and anion gap of urine. The essentials of urinalysis are discussed below.

Urinalysis (UA)

Given its simplicity and clinical relevance, UA is one of the most commonly performed clinical laboratory tests throughout the world. It is often the starting point in the clinical evaluation of patients with hypertension, renal insufficiency, urinary tract symptoms, or proteinuria. An expert evaluation of UA may distinguish glomerular from tubulo-interstitial disorders in the patients with elevated SCr levels and/or proteinuria. In addition, UA can help in following the activity of disease in a variety of renal disorders. UA is often called a 'poor man's renal biopsy'. As mentioned above, UA can also help in evaluating tubular function with relatively simple testing.

UA requires collection of 10 to 15 ml of fresh urine specimen in a clean, disposable container, which should be sterile if the sample is to be sent for culture. The first urine void of the day is considered the best specimen for analysis. Urine obtained at this time is in its most concentrated form; its relative acidity aids in the preservation of casts and cellular elements. Urine should be examined immediately (or stored briefly at 4° C), to avoid bacterial overgrowth and chemical decomposition of the urinary sediment.

Routine UA consists of three parts: evaluation of physical characteristics of urine, dipstick evaluation of urine, and microscopic examination of urine.

Evaluation of the Physical Characteristics of the Urine

The physical and chemical characteristics of urine and their significance are summarized in Table 3. Color of normal urine can range from yellow to amber, as a function of concentration of urine or osmolality. The osmolality of urine is determined by the number of particles in solution independent of their charge, size or density. This can be measured by freezing point depression by the lab, if needed. On the other hand, specific gravity of the urine can be measured relatively easily by refractometer, and depends upon number, relative size and density of particles in urine. It correlates with osmolality, but not in a mathematical fashion. The measurement of specific gravity by dipstick is not accurate. The physiologic range of urine specific gravity is 1.003 to 1.035 (compared to 1.000 for distilled water). Urine osmolality can ordinarily be increased by water deprivation, to a maximal capacity of 1200 mOsm/kg in a normal person, but cannot be achieved in states of deficiency of vasopressin. A good response to vasopressin will indicate deficiency of vasopressin (as in central diabetes insipidus) or resistance to action of vasopressin (as in nephrogenic diabetes insipidus). In those with low osmolality of plasma (due to relative excess of water compared to solutes), urine osmolality should be low, reflecting kidney's effort to excrete extra water. In the presence of hypoosmolar state, inability of kidney to dilute urine maximally (osmolality <100 or so), reflects presence of antidiuretic hormone, which may be appropriate (as in heart failure and cirrhosis) or inappropriate (as in those with syndrome of inappropriate antidiuretic hormone excess).

Semi-quantitative Chemical Analysis with a Dipstick Consisting of Multiple Test Reagents

Urinary pH can be measured rather accurately by dipstick and is usually within the range of 4.5 - 7.9. Urine pH can be alkaline after a meal (due to the "postprandial alkaline

Table 3. Urinalysis findings and their significance

	Characteristic	*Comment*
Color or Appearance	Pale (colorless)	Dilute urine (seen with polyuria, diabetes insipidus or diabetes mellitus)
	Turbid	Pyuria (seen with urinary tract infections)
	Red	Hematuria (seen with upper or lower urinary tract bleeding), beeturia, hemoglobinuria, myoglobinuria
	Yellow/Brown	Bilirubinuria
Specific Gravity	Very low	Dilute urine (seen with compulsive water drinking, beer drinking or diabetes insipidus)
	Very high	Concentrated urine or excess osmols (seen with pre-renal state, glucosuria, presence of mannitol or radiologic contrast agents)
Chemical Analysis (Dipstick)	Protein (+)	Measures albuminuria (suggestive of glomerular disorder)
	Glucose (+)	Either the renal threshold for glucose is exceeded (diabetes mellitus) or there is tubular disorder of glucose reabsorption. (Fanconi Syndrome)
	Blood (+)	Hemoglobinuria (seen with hematuria or hemolysis) or myoglobinuria (seen with rhabdomyolysis)
	Dip(+) / SSA(+)	Concordance between the two tests for proteinuria usually suggests albuminuria (indicative of glomerular disorder)
	Dip(-) / SSA(+)	Nonconcordance suggests Bence Jones proteinuria (as in multiple myeloma)

tide") and decreases with fasting. Urinary tract infection (UTI) with urea splitting organisms (especially proteus) and systemic alkalosis due to vomiting, diuretics or alkali therapy can render urine alkaline. It can be a clue to the presence of renal tubular acidosis. Persistently acid urine is seen with high protein intake (increased "fixed acid" generation), fever, gout, severe potassium depletion, hyperaldosteronism, metabolic acidosis (but not renal tubular acidosis- RTA), and cranberry juice ingestion.

Microscopic Evaluation of the Urinary Sediment

The microscopic examination is conducted on the pellet obtained after centrifugation of urine at 2000 revolutions per minute for 5 minutes. The supernatant should be saved for treatment with sulfosalicylic acid (SSA), if indicated. It is very useful and provides important clues to presence of intrarenal pathology. The typical findings are summarized in Table 3. Figure 1 shows examples of cellular elements found in the urinary sediment.

Red blood cells are not normally found in the urine. When present, they have the appearance of pale, biconcave disks. The margin is smooth and regular, but in hypertonic urine the cells will shrink and have a crenated (i.e., spiky) appearance. Dysmorphic (abnormally shaped) erythrocytes of acanthocyte variety indicate glomerular hematuria. Acanthocytes are doughnut-shaped or spherical (but microcytic) and have membrane blebs ("Mickey Mouse ears"). Leukocytes are larger in size and demonstrate the presence of cytoplasmic granules or lobulated nuclei. Presence of leukocytes usually indicates either infection (also associated with presence of bacteria) or interstitial nephritis. Epithelial cells may appear in the urine, and have different shapes according to the source they are derived from (renal tubular epithelium, transitional epithelium from the ureters or bladder, or squamous epithelium from the vaginal vault).

Urinary casts are formed in the distal tubule and collecting ducts. Particulate matter present in urine gets cast in the matrix of Tamm-Horsfall protein in the shape of renal tubules: cylindrical, with parallel sides and rounded ends. Identification of specific types of casts helps in narrowing the differential diagnosis in patients with renal disease (see Table 4). Granular or dense granular (muddy brown) casts signify tubular damage. Red cell casts (Fig. 2) or white cell casts (Fig. 3) indicate inflammation.

Measurement of Urine Electrolytes and Calculation of Urinary Anion Gap and Osmolal Gap

Urinary electrolytes should be measured in a randomly obtained (spot) urine sample. These can provide important information regarding the renal tubular concentrating ability, volume status, and even some acid-base and electrolyte disturbances. However, these should be interpreted in light of clinical setting. Low urine sodium level (less than 10 mEq/L) in a spot specimen generally indicates volume depletion or other pre-renal cause of acute renal failure (ARF). In excess of 40 mEq/L, it could suggest loss of proximal tubular concentrating ability (e.g., physical damage to the tubules, as in patients with acute tubular necrosis), but also adrenal insufficiency, recent diuretic use or renal insufficiency. When the spot urine sodium concentration is in the range of 10 to 40 mEq/L, it is useful to calculate a fractional excretion of sodium (FE_{Na}). The FE_{Na} can be calculated as:

$$FE_{Na} = (U_{Na}) \times (P_{creat})/(P_{Na}) \times (U_{creat})$$

Where U_{creat} and P_{creat} represent the urinary and plasma creatinine concentrations and U_{Na} and P_{Na}, urinary and plasma sodium concentrations, respectively. Values less than 0.01 (or 1 percent, if above formula is multiplied by 100) indicate low renal perfusion as in pre-renal ARF, sepsis, rhabdomyolysis, radiocontrast administration, nonsteroidal anti-inflammatory medicine use and acute glomerulonephritis. Values

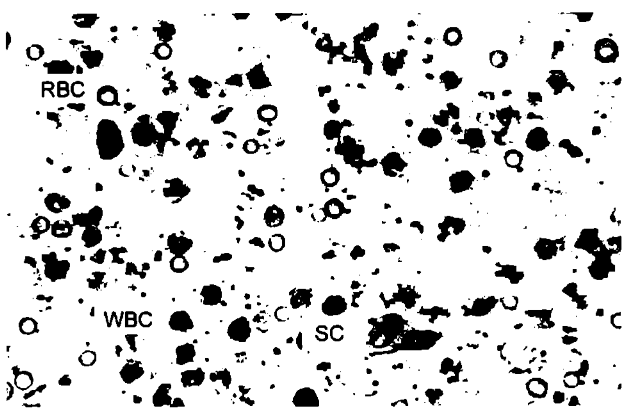


Figure 1: Cellular elements in urine. Red blood cells (RBCs) present as rounded cells without nucleus. White blood cells (WBCs) are slightly larger than the RBC and have granular appearance. Squamous cells (SCs) are large, irregular cells (*For color version, refer to plate 1*)

Table 4. Clinical significance of the urinary sediment findings

Element of Urinary Sediment			*Comment*
Cellular elements	Erythrocytes	Eumorphic	Bleeding form the upper or lower urinary tract, suggesting either renal or urologic disease
		Dysmorphic (abnormal shape)	Red cell abnormalities. Acanthocytes are indicative of glomerular bleeding, suggesting a glomerulopathy
	Leukocytes	PMNs	Inflammation of the upper or lower urinary tract, which can be infectious or not
		Eosinophils	Identified with Hansel's stain, suggestive of allergic interstitial nephritis (AIN)
	Epithelial cells	Tubular	Suggestive of tubular damage to the nephron; may be seen in early ATN
		Squamous	Typically seen with vaginal contamination of the sample
Urinary casts	Hyaline		Tamm-Horsfall protein; may be normal finding or suggestive of decreased renal perfusion
	Erythrocyte		Indicative of glomerular bleeding, suggesting a glomerulopathy/ glomerulonephritis (GN)
	Leukocyte		Inflammation of the renal parenchyma; seen with GN, AIN or pyelonephritis
	Granular	Fine	Actually a hyaline cast with granular matrix, suggestive of renal tubular damage
		Coarse	Densely pigmented ("muddy brown"); caused by sloughed tubular cells, suggestive of ATN
		Broad	May be caused by slow urine flow in dilated collecting ducts; suggestive of chronic renal insufficiency

PMN = polymorphonuclear leukocytes; ATN = acute tubular necrosis.

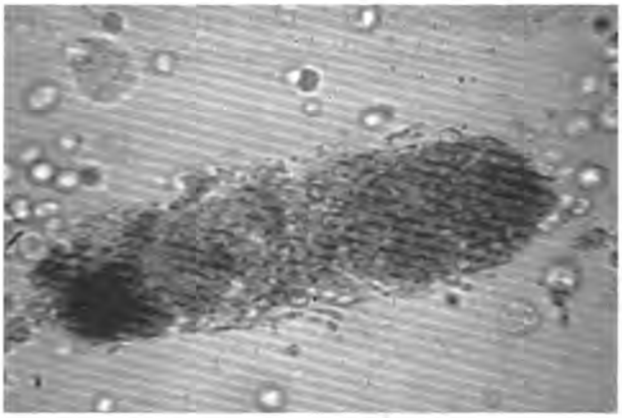


Figure 2: Red blood cell cast. Note numerous small RBCs packed within the cast, indicative of glomerular hematuria (*For color version, refer to plate 1*)

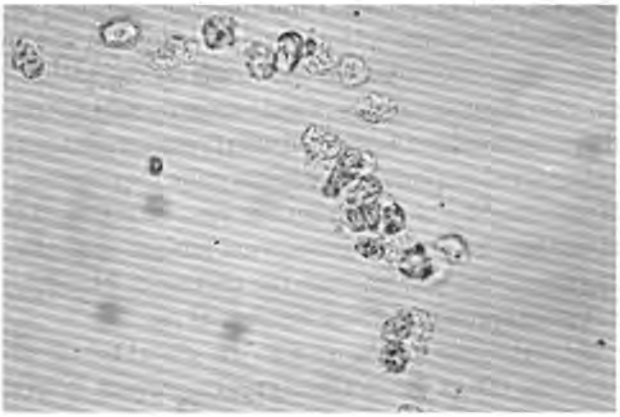


Figure 3: White blood cell casts. Note presence of multiple WBCs within the proteinaceous material in the shape of tubules (*For color version, refer to plate 1*)

greater than 1 percent or even higher may indicate acute tubular necrosis in an appropriate clinical setting of ARF.

Chloride levels, also measured by a spot test, may help differentiate between gastrointestinal and renal chloride wasting in the patients with metabolic alkalosis (values lower than 15 mEq/L suggest gastrointestinal losses). Although urinary chloride losses are usually associated with a spot urine chloride level in excess of 15 mEq/L, in cases of severe volume depletion associated with long-term diuretic use, the concentration may be lower. Urine chloride less than 20 mmol/L or greater than 20 mmol/L help in determining therapy of metabolic alkalosis.

Another useful measurement is the urinary anion gap, which may be used to distinguish between gastrointestinal and urinary bicarbonate losses in patients with hyperchloremic (normal anion gap) metabolic acidosis. The urinary anion gap is calculated as follows:

$$\text{Urinary anion gap} = (U_{Na} + U_K) - U_{Cl}$$

Which, as can be seen, is a function of the urinary concentrations (on spot urine test) of sodium, potassium and chloride, respectively. It is used to indirectly estimate the urinary ammonia (NH_4^+) excretion. Although direct urinary NH_4^+ measurement is possible, it is technically very difficult to perform and is not readily available. In chronic metabolic acidosis of nonrenal origin (e.g., diarrhea), the kidney will respond by increasing NH_4^+ production. This will result in an increase in Cl^- concentration, which will exceed the sum of ($Na^+ + K^+$). The urinary anion gap will then take a negative value. In contrast, the failure of the kidneys to excrete acid at a normal rate will result in metabolic acidosis (i.e., renal tubular acidosis). Then, urinary NH_4^+ is quite low, resulting in a positive urinary anion gap. Presence of ketoacids, hippurate, benzoate or penicillin derivatives may also make the urine anion gap positive. This is further discussed under Metabolic Acidosis.

Urine osmolal gap may be useful in the presence of unmeasured anions. It can be calculated as -

Urine Osmolal gap = Measured—Calculated urine osmolality.

Where,

calculated osmolality = 2x(Na+K)+(urea/2.8)+(glucose/18)

This can be simplified as $2xNa^+ + 10$ in those with relatively normal values of urea and glucose.

Proteinuria

Proteinuria is an important marker of renal disease. Normal urinary protein excretion is less than 150 mg/day. Of this, 60 percent is derived from filtered serum proteins (approximately 40 percent albumin, 15 percent immunoproteins, and 5 percent other plasma proteins) and 40 percent comes from the cells of the thick ascending limb of the loop of Henle (Tamm-Horsfall mucoprotein). Tamm-Horsfall protein forms the matrix of tubular casts. Transient proteinuria, independent of glomerular disease, can occur with fever, exercise, and upright posture (i.e., orthostatic proteinuria). Persistent proteinuria, however, has the significance of either glomerular or tubulo-interstitial renal disease. Glomerular proteinuria consists primarily of albumin and is often in the nephrotic range (>3 g/day). The term "microalbuminuria" is used for minor increases in urine albumin excretion (in excess of 30 mg/day). Albumin specific dipsticks can be used to detect microalbuminuria. First morning specimen is preferred for spot urine evaluation. Alternatively, spot urine albumin-creatinine ratio can be calculated. If the albumin excretion is in excess of 500 to 1000 mg/gm of creatinine, it is reasonable to follow proteinuria with spot urine protein-creatinine ratio. Quantitation of 24-hour urine protein excretion excludes the diurnal variation in protein excretion and remains the gold standard, though tedious and often impractical for the patient. SSA method (using a 20 percent SSA solution) precipitates all proteins present in urine (including Bence Jones proteins, glycoproteins, globulins, and albumin). It is important to do urine protein electrophoresis to rule out presence of monoclonal protein in most cases of proteinuria.

Immunologic Markers in Renal Disease

Autoimmunity is frequently involved in the pathogenesis of renal disease. Serology to measure markers of immune function is an important tool in differential diagnosis of renal, especially glomerular diseases. These will be discussed in detail in the chapter on glomerular diseases.

Radiologic Evaluation in Renal Disease

Radiologic studies are integral part of work up to define renal anatomy and perfusion. The studies should be chosen with discretion and should be individualized to obtain the most relevant information. Similar information can be obtained from different tests and there is no single best test for every patient.

In presence of renal insufficiency, it is important to consider the risks involved in a radiologic test. For example, use of radiocontrast media can result in loss of renal function and development of acute, and sometimes, permanent renal failure. Presence of renal insufficiency, older age, and amount and type of contrast are the most important risk factors for radiocontrast nephrotoxicity. Adequate hydration, use of isoosmolar contrast and premedication with certain medications may attenuate this insult. This will be dealt in more detail in the chapter on ARF.

Evaluation of Specific Renal Diseases

Depending upon the clinical circumstances, the most useful tests are outlined below:

Urinary Tract Infection

UTI, especially if confined to the lower tract, usually responds quickly to antibiotic treatment and there is no need for diagnostic imaging studies. The diagnosis of upper UTI (i.e., pyelonephritis) can usually be made clinically, but radiologic studies are needed in those with complicated pyelonephritis such as those with poor response to therapy, co-existing diabetes mellitus or altered immune state, known history of kidney stone or urinary tract abnormality with recurrent pyelonephritis. Patients with diabetes and pyelonephritis are at increased risk of emphysematous pyelonephritis, which is a particularly severe infection. Abdominal CT scan most effectively demonstrates the presence of air in a bubbled pattern in renal parenchyma and in Gerota's fascia. A nephrectomy is usually needed. Recurrent pyelonephritis in patients with a known history of stone disease can be evaluated by a renal ultrasound without using intravenous contrast.

Kidney Stone Disease

Asymptomatic urinary stones are often incidentally detected during an abdominal imaging study. Due to the presence of calcium in the urinary stones (85 t 90 percent), a plain abdominal radiograph of kidne bladder and ureter (KUB) region can detect stone (Fig. 4), but has a low sensitivity and specificity. An IV can also detect a radiolucent stone and presence o absence of obstruction, but has the disadvantage of usin radiation and contrast.

In the setting of renal colic, spiral CT scan (techniqu by which all the CT images are acquired in one breat hold, usually 20 seconds) will show virtually all kidne stones: both radioopaque and radiolucent, does nc require injection of contrast, and can be done quickl (Fig. 5). With evolving techniques, the dose of radiatio with spiral CT is expected to decrease.

Renal Masses

Renal masses are also commonly detected on radiologi studies performed for unrelated reasons. Abdomina CT, ultrasound, or MRI can further delineate the natur of the mass, which will impact treatment strategy. Fo example, a simple cyst detected by ultrasound must hav well-defined smooth walls, good enhancement, and n internal echoes; management consequently consists o periodic follow up only. Characteristics suggestive o malignancy such as lobular contour, poor enhancemen from the surrounding renal parenchyma, and presenc of calcifications warrant further investigation. A abdominal CT, by measuring the density of the mass a compared to that of water, can further define the cysts o

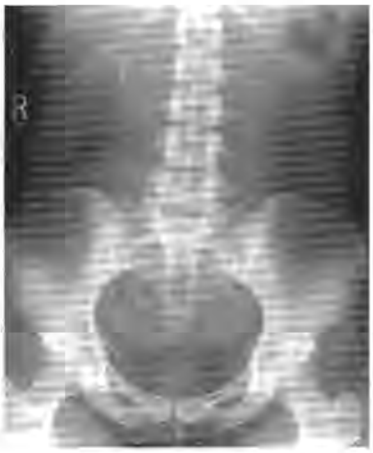


Figure 4: Kidney, Ureter, Bladder (KUB) film showing right renal stone. Radioopaque stones (due to the presence of calcium in the stone) can be detected by plain films

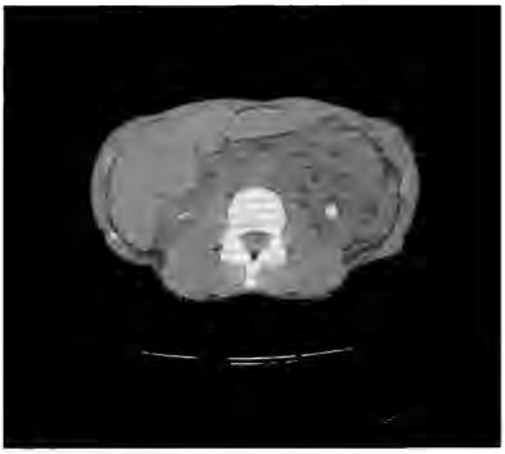


Figure 5: Spiral CT stone study showing presence of stones i both kidneys. The CT study has the advantage of having hig sensitivity and specificity, and no need of using radiocontrast

masses. A combination of studies, such as ultrasound, CT or MRI can be used for indeterminate lesions: often requiring periodic follow up. Figure 6 shows a simple renal cyst and figure 7 shows polycystic kidney disease.

Hematuria

Hematuria can occur from upper or lower urinary tract due to a variety of causes, such as glomerular disease, urinary stone, infection, or neoplasm. Due to its noninvasive nature, ultrasound can easily be used for initial evaluation of renal anatomy and presence of a lesion such as stone or mass. Retrograde pyelography is helpful in identifying and defining lesions in upper urinary tract. Cytology of urine should also be done to exclude malignancy. Cystoscopy is indicated to further evaluate the bladder if the hematuria is not explained by other tests. If these tests have still not determined the diagnosis, an abdominal CT or MRI with gadolinium can be performed as the next step.

Acute Renal Failure

Clinical evaluation of renal failure is usually accomplished by determining the cause as prerenal, intrarenal, or postrenal. The cornerstone of initial diagnosis of postrenal failure is the renal ultrasound. Postrenal failure is caused by bladder outlet obstruction (e.g., prostatic hypertrophy or tumor, neurogenic bladder, or bladder tumor) or bilateral ureteric obstruction (e.g., abdominal/pelvic mass or retroperitoneal fibrosis). A renal ultrasound will identify dilatation of the renal collecting system upstream from the blockage in most cases. Absence of dilatation or only minimal dilatation, despite the presence of obstruction, may indicate very recent obstruction. Retroperitoneal fibrosis can prevent development of obvious dilatation of renal pelvis despite causing ureteral obstruction. Dilated pelvis may also be a result of reflux from the bladder into the ureter and renal collecting system in the absence of actual obstruction. Chronic renal diseases are characterized by increased parenchymal echogenicity (brightness on ultrasound images) and small size of kidneys.

Renal Artery Stenosis

Renal artery stenosis (RAS) is a common, and potentially correctable, condition in patients with uncontrolled or atypical hypertension (early or late onset hypertension, rise in creatinine with ACE inhibitor treatment, presence of abdominal bruits, asymmetric kidneys by imaging), and unexplained renal insufficiency. A variety of radiologic tests can be used to screen for this anatomical condition in such patients, though the sensitivities and specificities of the tests vary with experience of operators. It is very important to determine the functional significance of the anatomical finding of a narrow artery before treating every such finding. While correction of stenosis with an invasive procedure may improve hypertension or renal insufficiency in some, the correction may fail to improve hypertension or renal insufficiency in others if chosen indiscriminately, and even prove to be hazardous. The added risk of contrast-induced

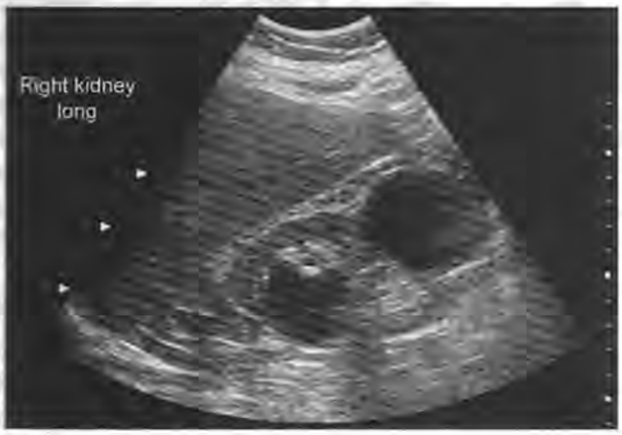


Figure 6: Simple renal cyst seen on ultrasound of the kidney. The cyst has thin walls, without internal echo, and is clearly demarcated from surrounding tissue

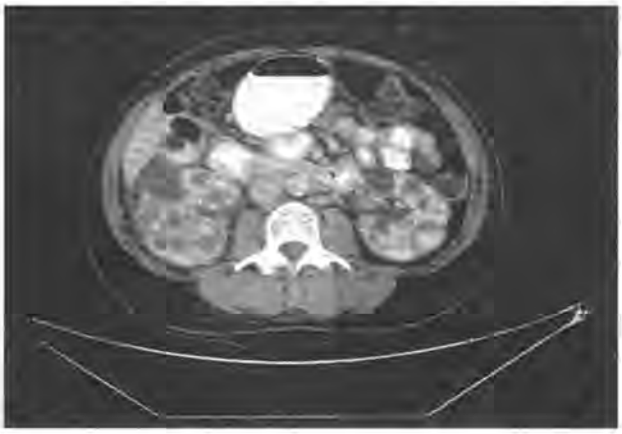


Figure 7: Bilateral multiple cysts shown by CT scan. The kidneys are enlarged with presence of innumerable cysts-characteristic of polycystic kidney disease

nephropathy superimposed on hypertensive damage is always a concern.

Duplex ultrasound is a relatively inexpensive and safe test (no exposure to radiation or dye), but it is difficult to visualize the entire main renal artery, particularly in obese patients. Vascular indices, such as resistive index of the blood vessel, have been suggested as a clue to the presence RAS. The accuracy of renal duplex ultrasound is highly variable and operator dependent and it is recommended for screening in those centers only that have proven its utility. Renal ultrasound in a patient with unilateral RAS may show increased renal parenchymal echogenicity and a difference in size between the affected (smaller) and unaffected kidney, but is not sensitive or specific. Magnetic resonance (MR) angiography has the advantage of avoiding the use of intravenous radiologic contrast media, but gadolinium-induced nephrogenic fibrosing dermopathy is a serious risk in those with decreased kidney function.

The gold standard for RAS evaluation remains conventional renal arteriography. It should probably be the first test when the clinical suspicion is high and the patient has normal renal function. It depicts the best anatomic detail of the renal arteries and provides an opportunity for treatment with balloon angioplasty. Figure 8 shows a renal arteriogram showing beaded appearance of bilateral renal arteries in fibromuscular dysplasia, a lesion found more commonly in young females, and amenable to renal angioplasty. However, renal angiogram is an invasive procedure and has a relatively high cost. It has the risk of atheroembolism and radiologic contrast induced nephrotoxicity, particularly in diabetics, older patients, and patients with pre-existing renal insufficiency. Therefore it cannot be used as a screening test for all patients, but rather in those where the index of suspicion is high.

Sampling of renal veins on both sides for measurement of renin can also be used to determine the site of production of renin.

Nuclear Imaging in Patients with Kidney Disease

Nuclear imaging is a method that uses a radioactive tracer which, when introduced into the body, targets a specific organ and emits a type of radiation that can be imaged and used for diagnostic purposes. The tracer consists of a radionuclide, most commonly ^{99m}Tc that is carried to the target organ by a nonradioactive pharmaceutical. Nuclear imaging provides physiologic data about the function of the organ of interest. Radiopharmaceuticals commonly used to target the genitourinary system are discussed in the Table 5.

Evaluation of the Renal Plasma Flow

DTPA or MAG3 may be used for evaluation of the renal artery flow and excretion. Relative GFR or ERPF can be calculated upon analyzing the flow down the aorta and into the renal arteries and the time taken for the radiopharmaceutical to concentrate into the renal cortex. Time-activity curves are also generated, showing the activity in each kidney during the time of the study.

Measurement of GFR

GFR can be measured using ^{99m}Tc -and DTPA is used to assess effective renal plasma flow (ERPF). Using nuclear medicine techniques, isotope counts are taken at about 1 to 2 minutes postdosing. The contribution by each kidney to total GFR or ERPF can be quantified. The information is very helpful in assessing differential function in asymmetrical renal disease as well as for monitoring changes in function over time. GFR measurements using nuclear medicine techniques correlate well with the inulin clearance and 24-hour Ccl measurements.

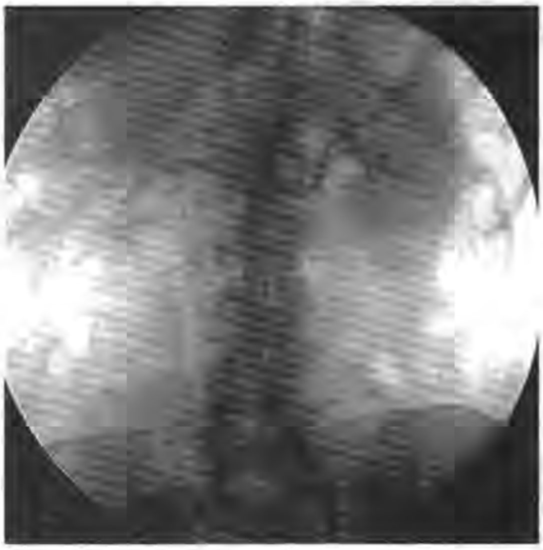


Figure 8: Renal arteriogram showing beaded appearance bilateral renal areries. The lesion was successfully angioplastie resulting in improvement in control of blood pressure

Table 5. Radiopharmaceuticals used in the evaluation of the urinary system

Radiopharmaceutical	*Comment*
^{99m}Tc Diethylenetriamine Pentaacetic Acid (DTPA)	Filtered 90% by the glomerulus. Used for measuring renal perfusion and excretion (rapidly cleared by the kidneys). Not useful when renal function deteriorates.
Orthoiodohippurate (OIH)	Used for measuring effective renal plasma flow (ERPF)
^{99m}Tc Mercaptoacetyltriglycine (MAG3)	Similar to OIH, but provides better image quality. Cleared primarily through the proximal tubules, it is the preferred agent in the patients with chronic renal insufficiency (CRI).
^{99m}Tc Dimercaptosuccinic Acid (DMSA)	Excellent for cortical imaging (high cortical retention). Can be used in assessing space-occupying lesions
^{99m}Tc Glucoheptonate	Also used for delayed cortical images.

Allergic Interstitial Nephritis (AIN)

Gallium-67 citrate is a radiopharmaceutical that accumulates in areas of inflammation; therefore it can be used to assess for AIN, as well as renal infections (e.g., renal and perirenal abscess) and tumors. The kidney usually excretes it within 24 - 48 hours from the time of administration. Retention beyond 72 hours, particularly in the setting of ARF, is suggestive (but not specific) of AIN.

Obstructive Uropathy

Presence of a dilated renal pelvis and/or collecting system by anatomic imaging studies, such as ultrasound, abdominal CT scan, or IVP may reflect previous abnormality, rather than ongoing obstruction. Presence of active obstruction can be assessed by diuretic-augmented renal scintigraphy (e.g., Lasix renal scan). After the administration of the diuretic, the urine flow increases and should clear the scintigraphic activity caused by a nonobstructed system. Time activity curves are generated for each kidney. Also, renal scintigraphic images can be analyzed and the clearance of nuclear "activity" is followed after the diuretic administration (Figs 9A and B.)

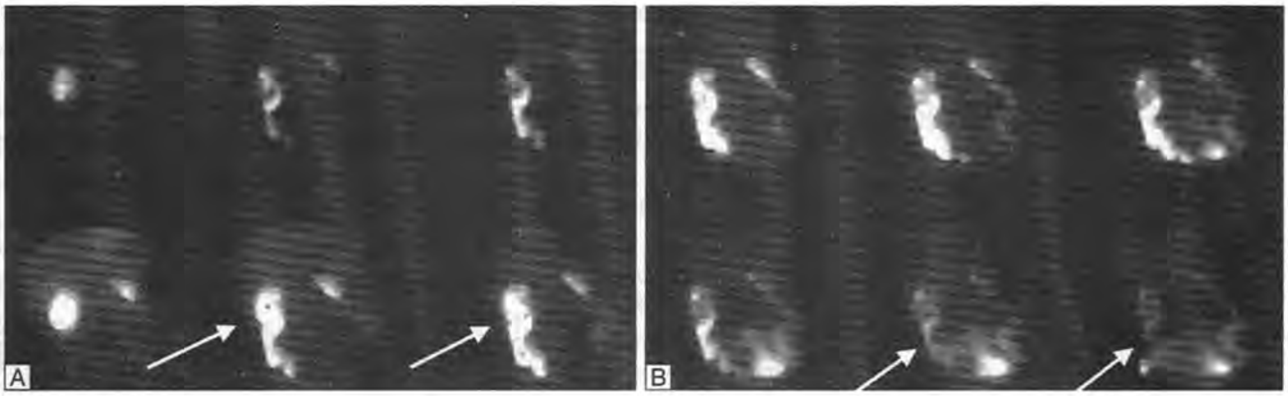
Renal Artery Stenosis

Secondary hypertension is often the result of renovascular disease, including major RAS. RAS may be atherosclerotic in nature (usually in older patients) or due to fibromuscular dysplasia, which is common in young females. The resulting fall in GFR leads to activation of renin-angiotensin system and maintenance of GFR via constriction of the efferent arteriole and increase in the intraglomerular pressure. The increased production of Angiotensin II results in HTN. Even when diagnosed, RAS is not always the cause of the HTN. Recent prospective clinical trials have failed to always show improvement in blood pressure control after treatment (e.g., balloon angioplasty with or without intra-arterial stent placement) for RAS. The captopril renal scan has been used (sensitivity of 89 to 94 percent and specificity of 89 to 96 percent) as a screening measure for hemodynamically significant RAS. The test simply evaluates the response of the kidneys to ACE inhibition and helps to predict if RAS (when present) will respond to revascularization procedures. By blocking the conversion of angiotensin I to angiotensin II, captopril causes a fall in GFR in patients with renovascular HTN (Figs 10A and B). This is the rationale for performing the captopril renal scintigraphy. It will be discussed more in the section dealing with renovascular hypertension.

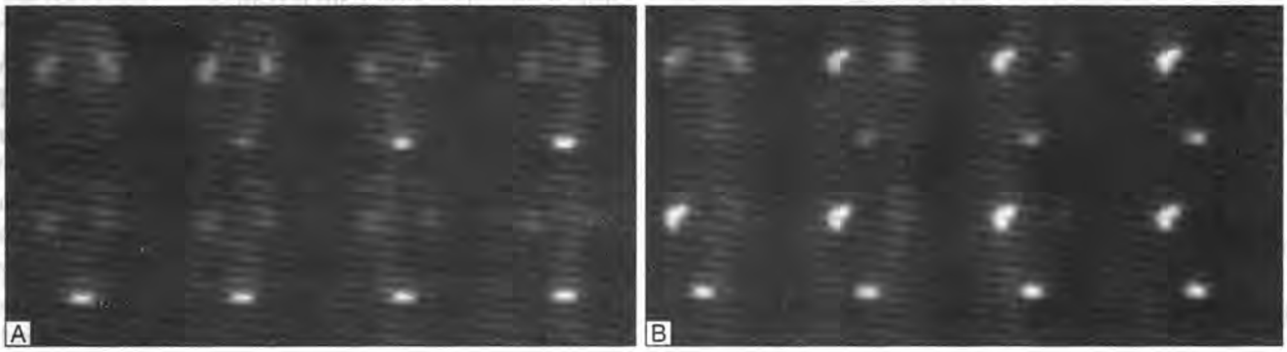
RENAL BIOPSY

Renal pathology can best be assessed by microscopic examination of renal tissue obtained by biopsy. The biopsy not only provides anatomical information, it provides diagnostic and prognostic information as well. Indications for renal biopsy include unexplained elevation of creatinine, proteinuria, hematuria, hereditary nephritis and in kidney transplant dysfunction.

The biopsy can be done by percutaneous technique using guidance of ultrasound or CT scan. Transjugular biopsy can be done in situations where it is not possible to reach the kidney from percutaneous route, or the patient is not able to cooperate during the procedure. Open surgical biopsy is needed in a patient with single



Figures 9A and B: Renal scintigram showing a small right kidney and normal appearance of the left kidney (A). There is bilateral (worse on the left –white arrows-) dilatation of the collecting system. There is prompt clearance (B) after administration of intravenous Lasix (thus, no urodynamically significant obstruction)



Figures 10A and B: Captopril scan showing no difference in perfusion of both kidneys (left panel). After administration of captopril, the perfusion of left kidney decreases significantly, which is suggestive of renovascular disease

kidney.

Biopsy sample is studied by three principal methods:

1. Light microscopy typically employs hematoxylin and eosin stain to examine the various structures in the parenchyma. Special stains such as silver stain, Masson trichrome, PAS, etc. are used as needed.
2. Immunofluorescence is a valuable method to detect immune complexes and antibodies mainly in the glomeruli, but in any part of the parenchyma. In some instances, this method may provide pathognomonic findings in certain diseases, e.g. anti-GBM antibody disease. Monoclonal antibodies labeled with fluorescent dyes are utilized to bind to various immune complexes or antibodies and studied under fluorescence microscope.
3. Electron microscopy examines the ultrastructure of the renal tissue and the cytoskeleton. Among its many benefits, this technique can detect the specific location of immune complexes within the glomeruli, examine basement membrane pathologies, detect viral particles in infectious diseases, etc.

SUGGESTED READING

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2. Investigation of renal disease. section 2: comprehensive clinical nephrology. Feehally and Johnson (eds) Mosby 3rd edition, 2007.

2

Physiology of Urinary Concentration and Dilution and Diabetes Insipidus

Karen S Servilla, Antonios H Tzamaloukas

The mammalian kidney possesses the ability to dissociate the excretion of water from the excretion of solute by varying urinary solute concentration (osmolality). The dissociation of water and solute excretions is made feasible by two features: (a) The unique anatomic and functional characteristics of the nephron parts which are responsible for urinary dilution and concentration, and (b) the anatomical and functional integrity of the regulatory mechanism for urinary concentration (vasopressin release). These two features must be understood before any study of the clinical disorders of urinary concentration and dilution is undertaken.

PHYSIOLOGY OF URINARY DILUTION AND CONCENTRATION

Unlike the apparently chaotic arrangement of the convoluted tubules in the renal cortex, the anatomical arrangement of the renal medulla appears orderly even on cursory examination. Descending limbs of Henle are closely apposed to ascending limbs and to bundles of vasa recta, whereas the interstitium is highly organized. The anatomical proximity of the structures with countercurrent flows of tubular fluid and blood, plus the solute and water permeabilities and transport characteristics of each nephron segment and vessel, allow fluid and solute exchanges between ascending and descending medullary structures. These exchanges are of paramount importance in the generation and maintenance of medullary interstitial hypertonicity and, therefore, in the elaboration of concentrated urine. A study of osmolality in the different nephron parts reveals the anatomical location of the diluting and concentrating nephron segments.

Osmolality of Tubular Fluid

Absorption of fluid in the convoluted parts of the proximal tubule is approximately isotonic. Therefore, plasma and proximal tubular fluid osmolalities are approximately equal. Figure 1 shows tubular fluid osmolalities in the renal medulla. Tubular fluid becomes progressively more hyperosmolar as it descends through the straight segment of the proximal convoluted tubule and the descending limb of Henle towards the tip of Henle's loop. In these segments, tubular fluid hyperosmolality is created by two mechanisms: (a) Osmotic transfer of water from the tubular lumen into the hypertonic medullary interstitium, and (b) Addition of solute, mainly sodium chloride and urea plus, to a much smaller extent, potassium salts, from the interstitium into the tubular lumen. The quantitative contribution of each of the two mechanisms to the generation of tubular fluid hyperosmolality is still a point of debate.

After tubular fluid passes through the tip of Henle's loop, tubular fluid osmolality decreases progressively in the ascending parts of the loop (only juxtamedullary nephrons possess both thick and thin ascending limbs of Henle; cortical nephrons possess only thick ascending limbs). The ratio of cortical to juxtamedullary nephrons is 7:3 in humans. In contrast to descending loop of Henle, water permeability in the thick ascending segments of

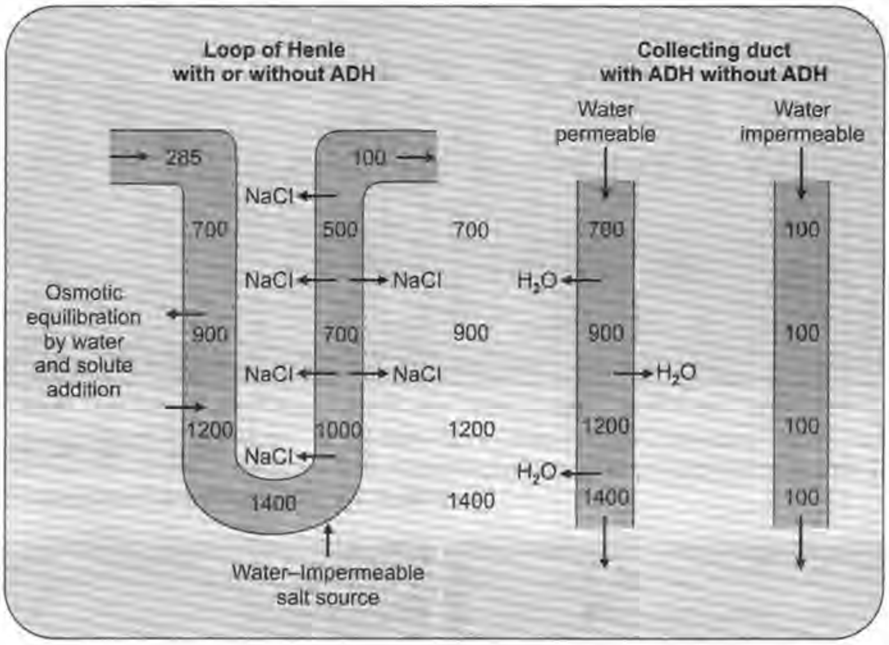

Figure 1: Tubular fluid osmolalities in the loop of Henle and collecting ducts and the effect of vasopressin. Interstitial medullary osmolality is equal to the osmolality of the corresponding level of the descending limb of Henle *(Reproduced with permission from Diseases of the Kidney, RW Schrier, CW Gottschalk, editors, 4th edition, Little, Brown and Co, Boston, 1988)*

Henle's loop is exceedingly low regardless of plasma vasopressin level. Furthermore, the ascending segments of the limb of Henle have high permeabilities for the solutes making up the bulk of the osmotic concentration in the tubular fluid in these segments (chloride, sodium, urea), and possess, at least in the thick ascending limb of Henle, potent mechanisms of solute transfer, such as Na-K-2CI cotransporter and Na-K ATPase. The progressive decrease in tubular fluid osmolality in these segments is, therefore, mediated through solute, mainly sodium chloride, transfer from the tubular lumen into the medullary interstitium.

As tubular fluid osmolality decreases progressively in the ascending limb of Henle, it reaches a point where it becomes equal to plasma osmolality. From that point on, further reduction in tubular fluid osmolality results in the elaboration of a progressively more hypotonic fluid. In physiologic states, the tubular fluid that issues out of the macula densa is always hypotonic to plasma. Administration of loop diuretics poisons the transport of chloride salts out of the thick ascending limb of Henle. This is the only way known to inhibit the elaboration of this hypotonic tubular fluid. The part of the ascending limb between the point where the tubular fluid becomes isotonic and the macula densa constitutes the main diluting segment of the kidney. The very low water permeabilities of the ascending parts of Henle's loop allow the creation of significant differences in osmolality between tubular fluid and surrounding medullary interstitium. At any transverse level through the renal medulla, interstitial fluid osmolality is substantially higher than the osmolality in the ascending limb of Henle.

In water diuresis, tubular fluid osmolality decreases further between macula densa and renal papilla. The mechanism of this further dilution of tubular fluid osmolality is also solute removal, as there is evidence supporting the view that water is transferred osmotically from the tubular lumen into the hypertonic interstitium even in water diuresis (water permeability of the collecting ducts is substantial even in the absence of vasopressin). Under antidiuretic conditions, however, water permeability of the collecting ducts, particularly of the inner medullary segment, is greatly increased under the influence of vasopressin. Therefore water transfer out of the collecting ducts into the hypertonic interstitium is greatly facilitated, and the urine becomes hypertonic. The collecting ducts constitute the concentrating segment of the nephron.

Osmolality in Renal Medulla

Under physiologic conditions, there is always an axial osmotic gradient in the renal medullary interstitium (Fig. 1). Interstitial fluid osmolality, which is equal to plasma osmolality in the renal cortex, progressively increases in the renal medulla between the cortico-medullary junction and the tip of the renal papilla. Since urinary concentration is obtained by passive transfer of water from the tubular fluid into the hypertonic medulla, the generation and maintenance of the interstitial axial osmolality gradient in the renal medulla is indispensable for the medullary interstitial hyperosmolality. It is made up by sodium chloride and, in the inner medulla, primarily by urea. The generation and maintenance of the axial osmolality gradient in the renal medulla requires energy expenditure. The energy sources for this function are provided by the different sodium (and potassium) chloride pumps present in the epithelial cells of the ascending limbs of Henle. The main energy source is the Na-K ATPase of the basolateral membranes of the tubular cells. The effect of the energy expenditure is amplified by the transfer of solutes and water between structures with countercurrent flows (ascending and descending tubules, blood vessels). The low medullary blood flow, particularly in the inner medulla, in comparison to the cortical blood flow, prevents the rapid transfer of solutes entering the vasa recta by the countercurrent process away from the renal medulla and, therefore, the dissipation of the medullary hypetonicity.

The Countercurrent Mechanism of Urinary Concentration

The countercurrent arrangement had been applied in engineering for the construction of devices requiring local concentration of a physical property, heat for example. After the description of the urinary countercurrent concentrating mechanism by Kuhn, countercurrent arrangements of structures with specific functions were found in many species and organ systems (example: Prevention of dissipation of heat loss from the legs of penguins touching cold soil). The countercurrent mechnism requires a single effect (transfer of a solute species out of an ascending structure in the case of urinary concentrating mechanism) and a multiplication of this effect by passive countercurrent transport. In the outer medullary thick ascending limb of Henle, the single effect is provided by active transport of sodium chloride out of the tubular lumen. Neither the mechanism, active or passive, nor the exact site of the single effect in the inner medulla are agreed upon. A detailed analysis of the proposed single effects and of the mathematical models of the countercurrent multiplication system in the kidney is beyond the scope of this chapter. A concise and informative analysis of this topic was published recently.

Quantitative Description of Urinary Concentration and Dilution

Unlike the mathematical models of the countercurrent multiplication system, the quantitative description of urinary dilution and concentration is relatively simple. If C_{Osm} is total urinary solute clearance, V the urine volume, U_{Osm} the urinary solute concentration, and P_{Osm} the plasma solute concentration (osmolality), C_{Osm} can be expressed by the classical clearance formula:

$$C_{Osm} = \frac{U_{OsmV}}{P_{Osm}} \qquad [1]$$

If the urine is more dilute than plasma ($U_{OSm} < P_{Osm}$), free water clearance (CH_2O = the volume of water that would be needed to be added to an isotonic solution containing exactly the amount of solute present in the urine to produce a final osmolality equal to U_{Osm})is:

$$CH_2O = V - C_{Osm} = V(1 - U_{Osm}/P_{Osm}) \qquad [2]$$

If the urine is more concentrated than plasma ($U_{Osm} > P_{Osm}$), negative free water clearance (TcH_2O = the volume of water needed to be removed from an isotonic solution containing exactly the amount of solute present in the urine to produce a final osmolality equal to U_{Osm}) is:

$$TcH_2O = C_{Osm} - V = V(U_{Osm}/P_{Osm} - 1) \qquad [3]$$

A more precise notation of equations 2 and 3 substitutes the sum of major electrolytes excreted in the urine, sodium (U_{Na}) and potassium (U_K) for osmolality, as follows:

$$CH_2O = V(1-[U_{Na} + U_K]/P_{Na}) \qquad [4]$$

$$TcH_2O = V([U_{Na} + U_K]/P_{Na}-1) \qquad [5]$$

Another useful notation is the minimal and maximal urinary osmolality that can be achieved by normal kidneys. Whereas the minimal urinary osmolality, which is around 50 mOsm/kg, differs little between species, maximal urinary osmolality which reaches 1,200 mOsm/kg in the humans, varies greatly between species and can reach several thousand milliosmoles in some desert rodents, allowing them to conserve water more efficiently.

VASOPRESSIN RELEASE AND ITS MODE OF ACTION

Arginine vasopressin (AVP) is the antidiuretic hormone (ADH) of humans and most other mammals. It is a 1,100 dalton nonapeptide, synthesized as a much larger pro-hormone in the cell bodies of hypothalamic neurons located primarily in the supraoptic and paraventricular nuclei. The pro-hormone travels down neuronal axons through the pituitary stalk into the posterior lobe of the pituitary gland, where it is stored as complexes with neurohypophysis II. When the neuron is stimulated, the complexes are secreted into the circulation by exocytosis, and they separate after discharge freeing vasopressin in the circulation.

Vasopressin Release

Vasopressin is released under a variety of physiological and pathological stimuli. The chapter on hyponatremia and inappropriate ADH secretion describes the pathological stimuli of vasopressin release. The discussion in this chapter will be limited to the two stimuli that have proven physiologic significance, namely hypertonicity (increased effective osmolality) and hypovolemia. It is currently believed that vasopressin is the regulatory hormone of body fluid osmolality and plays a major role in the defense against hypovolemia.

Verney demonstrated the effect of local hypertonicity, created by infusion of small amounts of hypertonic solutions in the carotids of dogs, on urinary osmolality. He also demonstrated that intracarotid infusion of hyperosmolar solutions containing solutes freely crossing cell membranes (urea) failed to produce increased urinary osmolality. The osmoreceptors sensing plasma tonicity are most probably located in the hypothalamus close to the supraoptic nuclei. The development of vasopressin radioimmunoassay by Robertson allowed the exploration of the quantitative relationships between plasma osmolality and plasma vasopressin levels, and between plasma vasopressin levels and urine osmolality. These relationships provide strong support to the notion that vasopressin is the regulatory hormone of body fluid osmolality. In the physiologic range of plasma osmolality and vasopressin concentration (0-5 pg/mL), a change in plasma osmolality equal to one percent results in a change in plasma vasopressin concentration equal to one pg/mL. As a result of a one pg/mL change in plasma vasopressin concentration, urine osmolality changes by 250 mOsm/kg.

The afferent pathway for vasopressin release secondary to volume depletion starts with baroreceptors located in the aortic arch and carotid sinus. At low levels of volume depletion, this mechanism of vasopressin release is insensitive. The rises in plasma vasopressin concentration resulting from extracellular volume losses less than 10 percent are minor or none. However, extracellular volume losses exceeding 15 percent produce large increase in plasma vasopressin levels regardless of plasma osmolality.

Vasopressin Mode of Action

Vasopressin Receptors

Circulating vasopressin is bound to the receptors found in many organs, including kidneys, liver, brain and vascular smooth muscle. Vasopressin receptors belong to a family of integral proteins containing 371 amino acids, with seven membrane spanning sites. The amino-terminal is extracellular, while the carboxy-terminal is located intracellularly. These receptors are all G-protein coupled receptors for AVP and related hormones (e.g., oxytocin).

So far, three receptors for AVP have been cloned, inducing V1a (smooth muscle, liver) V1b (pituitary) and V2 (kidney). Stimulation of V1a and V1b receptors causes hydrolysis of phosphatidylinositol and intracellular calcium mobilization, while stimulation of V2 receptors causes intracellular release of cyclic AMP.

Five sites with vasopressin receptors have been identified in the kidney: the glomerular mesangial cells (V1a receptors), the vasa recta (V1a receptors), the medullary interstitium (V1a receptors), the epithelial cells of the medullary thick ascending limb of Henle (V2 receptors), and the basolateral (antiluminal) membranes of the principal cells of the collecting ducts (V2 receptors). The intercalated cells of the collecting ducts have no AVP receptors. In several of these sites, such as the mesangial cells, vasopressin has trophic and functional effects.

In contractile cells (mesangium, vasa recta), vasopressin-induced increases in intracellular calcium concentration result in myosin phosphorylation and contraction. Contraction of vasa recta reduces the dissipation of medullary interstitial solute and assists in the maintenance of medullary hypertonicity. In mesangial cells and medullary interstitial cells, the vasopressin-induced intracellular release of calcium stimulates synthesis of prostaglandin E, which modulates vasopressin-induced water absorption. In the medullary thick ascending limb of Henle of several animal species, vasopressin induced increase in cyclic AMP increases the number of potassium channels and Na-L-2CI cotransporter units in the apical membrane, thus contributing to the increased reabsorption of chloride salts. Increased transfer of chloride salts outside the lumen of the medullary thick ascending limb of Henle increases medullary hypertonicity. However, the site of the major action of vasopressin on urinary osmolality is the collecting duct.

An important development was the cloning of the gene for the V2 receptor, located in the X-chromosome, and the subsequent cloning of the mutant V2 genes from patients with sex-linked variant of congenital nephorgenic diabetes insipidus. The loss of function of the mutant V2 receptor, analyzed by in vitro protein expression technology, is thought to be secondary to impairment of the binding of AVP at the cell surface, or blocked intracellular transfer of the message from the activated receptor, or ineffective synthesis and/or accelerated degradation of the receptor.

Water Channels

The discovery of the water channels in the cell membranes was a major step in deciphering the mechanism of water transfers in the body. The first description of a 28 kd, 271 amino acid integral protein spanning the wall of red cells in six sites, with intracellular location of both the amino and the carboxy-terminal was published from the laboratory of Dr Agre in John Hopkins in 1988. This protein was found to have substantial homology with membrane proteins found in many animal organs. Such proteins are channels. The same group of investigators performed the critical experiment establishing the new protein as a water channel. After this last experiment the new protein was called aquaporin (AQP). Subsequently, there were several aquaporins discovered in mammalian tissues and several others in tissues of other species including bacteria. Some of the "other" aquaporins were shown to be channels not only for water, but also for other small molecular weight substances (e.g. glycerol).

The original aquaporin (AQP1) is found in the cell membranes of erythrocytes, brain cells, endothelial cells, lung cells and other tissues. In the kidney, both the apical (luminal) and the basolateral (antiluminal) membranes of the epithelial cells of the proximal convoluted of AQP1, which is constitutive and is not regulated by AVP, is the cause of the high water permeability of these segments. Mutations of the AQP1 gene are associated with a mild form of congenital nephrogenic diabetes insipidus.

Of interest to the renal concentrating mechanism and its clinical disorders are the renal aquaporins AQP2, AQP3 and AQP4, which are located in the principal cells of the collecting ducts. AQP3 and AQP4 are located in the basolateral membrane. Under conditions of water diuresis (low plasma AVP levels), AQP2 is located primarily in the cytoplasm and only a small fraction of the total AQP2 molecules is inserted in the apical membrane. In antidiuresis (high plasma AVP levels), AQP2 is located in the apical membrane. AVP, therefore, controls the number of AQP sites in the apical membrane of the principal cells of the collecting duct.

The apical membrane is the rate limiting site for water transfer in the collecting ducts. Figure 2.2 summarizes the current understanding of the transduction of the AVP signal in a principal collecting duct cell. AVP binds to the V2 receptor in the basolateral membrane activating the V2 receptor/G-protein complex, which then activates adenylate cyclase leading to increased cyclic AMP production. The high cyclic AMP levels activate protein kinase A, which causes phosphorylation of cytoplasmic AQP2 at serine 256, a site close to the carboxy-terminus. Prostaglandin E2 inhibits AVP-induced increased water permeability of the collecting ducts by reducing cyclic AMP levels.

The phosphorylated cytoplasmic AQP2 molecules migrate toward the apical membranes along the microtubules, which are dipoles with the negative pole oriented towards the apical membrane. The cytoplasmic migration of phosphorylated AQP2 involves dynein, a minus-end directed motor protein, and dynactin, a protein complex facilitating the association of AQP2 with dynein.

The next step is insertion of the phosphorylated AQP2 in the proper site of the apical membrane. This step involves the SNARE system (soluble NSF attachment protein receptors), which was first described in neuronal cells. The SNARE system involves proteins attached to the AQP2 vesicles (VAMP-2) and membrane proteins (syntaxins). After dissipation of the AVP effect, cyclic

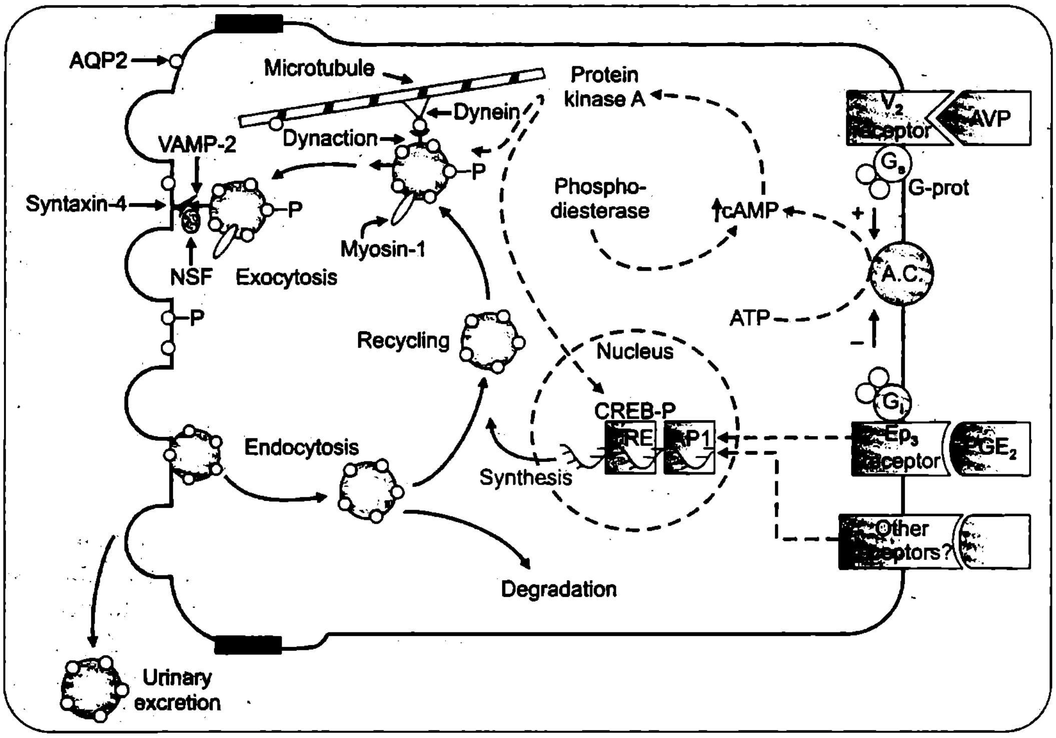

Figure 2: Signal transduction of arginine vasopressin in the principal cells of the collecting duct *(Reproduced with permissio from Nielsen S, et al. Physiology and Pathophysiology of Aquaporins. J Am Soc Nephrol 10: 645-766, 1999)*

AMP levels decrease and apical AQP2 levels are dephosphorylated and then migrate back into the cytoplasm. The increase in the permeability of the apical membrane to water under the influence of AVP is the result of the increased number of phosphorylated AQP2 in this membrane. Water entering the principal cells through the AQP2 sites exits the cells through the basolateral AQP3 and AQP4 channels.

The onset of action of vasopressin on water permeability of the collecting duct is rapid, within seconds of its addition. Vasopressin also enhances urea permeability of the collecting ducts, probably through stimulation of the synthesis of a urea transporter.

ABNORMALITIES OF URINARY CONCENTRATION

Renal disease, abnormalities in vasopressin release, or abnormalities in water balance, including thirst abnormalities, can alter the regulation of serum tonicity. This chapter will study abnormalities in urinary concentration. Abnormalities of urinary dilution are studied elsewhere in this book. Urinary concentratin ability is diminished by conditions affecting eithe vasopressin release (central or pituitary diabete insipidus), or renal response to vasopressin (nephrogeni diabetes insipidus). The cardinal clinical manifestation both syndromes is polyuria with dilute urine. The wat deprivation test is currently the method of choice for t differentiation the three polyuric states presenting wit dilute urine.

The water deprivation test is performed by withholdi water after the patient is well hydrated and by freque (hourly) measurements of body weight and urine a serum osmolality. The test is completed (or terminate when the patient loses three percent of body weig (5% of body water), which should produce a maxim physiologic response in vasopressin release. T test, which requires 10-12 hours for its completion normals, can take a much shorter time for patien with abnormalities in urinary concentration. It requir constant monitoring of the patients, because dehydrati can become severe in patients unable to conserve wat The important findings at the end of this first phase of t

Table 1. The water deprivation test

Clinical state	*Water Deprivation*		*Endogenous ADH*	*Exogenous ADH*
	*POsm**	*UOsm**	*Plasma level**	*Effect on U_{Osm}*
Normal	> 3% rise	> 800	High	None
Central DI				
Complete	> 3% rise	< 200	Absent	Increase> 30%
Partial	> 3% rise	300-700	Low	Increase> 10%
Nephrogenic DI				
Congenital	> 3% rise	< 300	High	None
Acquired	> 3% rise	300-500	High	None
Primary (Psychogeny)				
Polydipsia	> 3% rise	> 600	High	Increase < 10%

P_{Osm} = Plasma osmolality (mOsm/kg)
U_{Osm} = Urine osmolality (mOsm/kg)
DI = Diabetes insipidus
*= at end of water deprivation period, prior to exogenous vasopressin administration

test consist of a 5 percent increase in serum osmolality to ensure maximal physiologic stimulation of vasopressin release, measurement of urine osmolality to assess the effect of dehydration on the urinary concentrating mechanism, and a plasma vasopressin level. The test can be interpreted even when vasopressin measurements are not available, by administering exogenous vasopressin after the end of the first phase and recording the ensuing changes in urine osmolality. Table 1 shows the differentiation of the polyuric states with dilute urine by the water deprivation test and administration of exogenous vasopressin.

Central Diabetes Insipidus (Central DI)

Table 2 shows the etiology of central DI. In half or more than half of the cases with central DI, no cause can be ascertained (idiopathic). Brain trauma, surgery, and tumors, primary or metastatic, account for the majority of the cases with known etiology. After brain surgery, urinary concentration and dilution abnormalities often follow a triphasic course, with an early phase of DI from destruction of the neurohypophysis followed in a few days by a phase of inappropriate ADH secretion due to the release of stored vasopressin. After another few days during which vasopressin stores are depleted, permanent DI is established. Breast carcinoma is the most common metastatic tumor causing central DI. In the congenital form of the syndrome, which is inherited as an autosomal dominant or a sex-linked recessive condition, a selective depletion of neurosecretory granules appears to develop in the supraoptic and paraventricular nuclei. The autosomal dominant variety is caused by mutations in the gene coding the vasopressin-neurohypophysis precursor. The X-linked variants has not been completely characterized.

Clinically, complete central DI manifests with polyuria, up to 10 liters or more of dilute urine daily, and severe thirst. Polyuria and thirst persist unabated at night. Plasma osmolality and sodium concentration tend to be on the high side of the normal range in ambulatory patients with free access to water. If patients become

Table 2. Causes of central diabetes insipidus

1. **Congenital**
   - Autosomal recessive
   - Sex-linked
2. **Idiopathic**
   - More than 50% of all cases
3. **Other causes**
   - Brain tumors (benign, malignant)
   - Metastatic brain tumors (breast)
   - Meningioma
   - Head trauma, surgery
   - Brain thrombosis, hemorrhage, aneurysms
   - Infections (meningitis, encephalitis, Guillain-Barre syndrome)
   - Granulomatous disease (tuberculosis, sarcoidosis, histiocytosis)

bedridden, confused, or unable to consume water freely for whatever reason, severe hypernatremia with neurologic manifestations can develop rapidly. For this reason, comatose patients, particularly after head trauma or brain surgery require monitoring of urine volume, urine osmolality and plasma sodium concentration. In some instances, prolonged polyuria of the magnitude of 10 liters daily leads to bladder dilatation, hydroureters and hydronephrosis.

The management of central DI includes management of water and drugs. Some patients with a partial defect in AVP secretion and intact thirst mechanism can be managed by increased intake of water only. Water intake is divided day and night to avoid nocturnal dehydration. Other patients with partial central diabetes insipidus can be managed by drugs which either stimulate vasopressin release or enhance its action on the collecting ducts. Chlorpropamide in a dose of 250 mg once or twice a day, or clofibrate in a dose of 500 mg four times a day, or a combination of the two drugs, have been tried. Persistent hypoglycemia has led to failure of chlorpropamide treatment in several instances.

Several preparations of vasopressin are available for the treatment of central DI. Aqueous vasopressin is injected subcutaneously in a dose of 2-4 units every 6 hours. This preparation, which has a very short half-life (minutes), is used for comatose patients. Desmopressin acetate, which is a synthetic analogue of vasopressin with longer half-life (hours) is administered by nasal spray in a dose of 2.5 to 15 microorgans every 8 to 24 hours. Headache is the most common side effect of nasal desmopressin. Desmopressin can also be given subcutaneously or intravenously in a dose of 1-2 micrograms twice a day. Vasopressin tannate oil, which has the longest of half-life can be given as 2.5 units every 24 to 72 hours. Sterile abscesses of the injection sites have been reported in some patients receiving this preparation. Once vasopressin is started, patients should be cautioned to reduce fluid intake. Life-threatening hyponatremia can develop rapidly if large water intake continues while the kidney is obligated to elaborate a concentrated urine.

Nephrogenic DI

Nephrogenic DI is caused, in general, by two mechanisms: Loss of medullary hypertonicity because of anatomic disease of the kidney or functional disturbances, and inability of the collecting duct epithelium to respond to vasopressin. Table 3 shows the causes o nephrogenic DI. The most common form of congenita nephrogenic DI is inherited by an X-linked recessive pattern. Affected males manifest the condition from birth consisting of dehydration, hypertonicity, seizures and if the condition is not diagnosed on time, failure to thrive and mental retardation. Hydronephrosis enuresis and urinary infections are also encountered frequently. Female carriers demonstrate inability to adequately concentrate the urine under condition of water deprivation, but are usually asymptomatic This form of congenital nephrogenic DI is caused by mutations in the gene of the V2 receptor. More rare forms, inherited as autosomal recessive or autosoma dominant, are caused by mutations in the AQP2 gene which is located in chromosome 12. The managemen of the condition includes adequate water administration throughout the 24 hours plus thiazide diuretics which block urinary dilution.

Table 3. Causes of nephrogenic diabetes insipidus

1. Absent or decreased collecting duct response to vasopressin
    - a. Congenital nephrogenic diabetes insipidus
        - Sex-linked
        - Autosomal recessive
        - Autosomal dominant
    - b. Drugs
        - Lithium, demeclocycline, amphotericin B, methoxyflurane
    - c. Hypokalemia
    - d. Hypercalcemia
2. Loss of medullary hypertonicity
    - a. Diseases affecting the renal medulla
        - Pyelonephritis, papillary necrosis, analgesic nephropathy, medullary cystic disease, polycystic kidneys, Sjögren's syndrome, amyloidosis, sarcoidosis, multiple myeloma
    - b. Drugs
        - Loop diuretics
    - c. Starvation
    - d. Postrenal transplantation
3. Mixed pathogenesis (unresponsiveness to vasopressin plus loss of medullary hypertonicity)
    - a. Chronic renal failure
    - b. Postobstructive diuresis
    - c. Sickle cell disease

Acquired forms of nephrogenic DI are partial. The kidneys can respond to vasopressin by raising urinary osmolality to 300-500 mOsm/kg. Polyuria, therefore, is modest (3-5 liters per day) in these syndromes, and severe dehydration with hypertonicity is unlikely, except in comatose patients. AQP2 expression is decreased in all chronic forms of acquired nephrogenic DI.

Among the drugs listed in Table 3 as causes of nephrogenic DI, two, lithium and demelocycline, have great clinical importance. Lithium is used extensively in the management of the manic phase of the bipolar psychiatric illness. It produces polyuria routinely, and patients or their guardians should be warned about this side effect and the need for increased water intake during treatment. Lithium blocks adenylate cyclase and obliterates AQP2 expression. Demeclocycline, which also inhibits adenylate cyclase and at a site distal to cyclic AMP formation, is useful in the management of the inappropriate ADH secretion syndrome. Although, some reduction in medullary hypertonicity is present in both hypokalemia and hypercalcemia, it appears that the main mechanism of nephrogenic diabetes insipidus in both these conditions is a decreased response of the renal collecting ducts to vasopressin.

Renal diseases which disrupt the anatomic integrity and function of the renal medulla, or lead to relative increases in the medullary blood flow, lead to partial forms of nephrogenic diabetes insipidus, while diluting ability of the kidneys, in general, is preserved. Table 3 lists the important renal conditions associated with nephrogenic DI. Loop diuretics decrease medullary hypertonicity by inhibiting its energy source (chloride pumps). Starvation leads to urea depletion and to low glomerular filtration rate with consequent low rate of chloride salt absorption at the ascending limb of Henle. In the first few days after renal transplantation and after correction of urinary obstruction, urinary concentrating ability is impaired because of large osmotic diuresis.

The inability to concentrate the urine in advanced renal insufficiency is due, at least in part, to disruption of the anatomy of the renal medulla and to increased solute load (osmotic diuresis) per functioning nephron. However, there is evidence that the epithelium of the collecting ducts from experimental animals with chronic renal failure does not respond appropriately to vasopressin. Post-obstructive diuresis is due to osmotic diuresis, to a large extent. However, decreased medullary hypertonicity, increased medullary blood flow, and decreased epithelial response to vasopressin, probably mediated by increased production of prostaglandin E2, contribute to the decrease in renal concentrating ability in this syndrome. Finally, in sickle cell disease or trait, destruction of the medullary anatomic structure is the most probable cause of nephrogenic DI. However, the concentrating defect is reversible, at least in the early stages. It appears, therefore, that other factor such as, increased renal medullary blood flow, and, possibly, changes in the responses of the epithelium of the collecting ducts to vasopressin may contribute to the concentrating defect that is present in subjects with sickle cell disease or trait.

The management of nephrogenic DI is symptomatic. Large amounts of water and salt, divided throughout the 24 hours, should be administered to prevent dehydration. For most of the clinical states discussed, including chronic renal failure and post-obstructive diuresis, diluting ability is maintained while concentrating ability is severely impaired. In these instances, inhibiting the diluting mechanism with thiazide diuretics can be helpful. If the underlying condition (drugs, multiple myeloma, sarcoidosis, etc.) is treatable, treatment of the condition may ameliorate or reverse the renal concentrating defect.

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3

Hyponatremia: Etiology, Pathophysiology, and Management

Anil K Mandal

DEFINITION

Hyponatremia, by definition, is a serum sodium concentration of less than 136 mmol/L (the normal level is 136 to 145 mmol/L). The serum sodium concentration is largely a reflection of total body water; therefore, changes in the concentration of serum sodium essentially reflect changes in body water. Hyponatremia is a common abnormality detected by laboratory tests and found in 15 to 25 percent of patients in general hospital settings. However, in most instances, patients are asymptomatic or only minimally symptomatic. Conversely, it is not uncommon to see a patient brought to the hospital emergency room because of neurologic manifestations, such as gross alterations in state of mind, convulsions, or coma, which are directly attributable to hyponatremia. In psychiatric wards of general hospitals and more often in psychiatric institutions, symptomatic hyponatremia is a common occurrence.

ASSOCIATED CONDITIONS

1. Hyponatremia can be associated broadly with three major types of conditions: Conditions associated with excessive accumulation of extracellular fluid. In these settings, hyponatremia usually is chronic and causes no symptoms. Typical examples include:
   a. congestive heart failure
   b. cirrhosis of the liver
   c. nephrotic syndrome
2. Excessive loss of sodium in the urine. Typical causes include:
   a. diuretic therapy: hydrochlorothiazide, loop diuretics
   b. medullary cystic disease of kidney
   c. chronic kidney disease
   d. hypertension (exaggerated natriuresis)
3. Inability to excrete free water, which is probably the most common cause of acute and symptomatic hyponatremia. Typical causes include:
   a. syndrome of inappropriate antidiuretic hormone (SIADH)
   b. compulsive water drinking (water intoxication)
   c. overzealous use of potent diuretics
   d. acute alcoholism
   e. postsurgery conditions
   f. drugs (a list of drugs that may produce hyponatremia mimicking SIADH are listed in Table 1).

Table 1. Drugs associated with hyponatremia

Anticancer drugs	Cyclophosphamide
	Vincristine
Antidepressants	Tricyclics
	Fluoxetine (Prozac®)
Antipsychotics	Chlorpromazine
Antidiabetics	Chlorpropamide
	Glyburide
Natriuretic agents	Diuretics
Central nervous system depressants	Morphine
Anticonvulsants	Carbamazepine

Less typical causes of hyponatremia include:

- severe dehydration from vomiting
- nasogastric suction
- diarrhea
- severe exercise (Marathon runners)
- malnutrition

Glucocorticoid Deficiency

Glucocorticoid deficiency results in a clinical picture almost indistinguishable from that of SIADH. Persistent arginine vasopressin (AVP) secretion in this condition is caused by loss of hypotonic suppression of AVP release, which may be occasioned primarily by glucocorticoid deficiency per se and aggravated secondarily by multiple nonosmotic stimuli, including nausea, hypotension, and hypoglycemia.

Severe Diuretic-induced Hyponatremia in the Elderly

Severe hyponatremia associated with neurological manifestations is observed among patients receiving thiazide or loop diuretics. There is some controversy regarding the prognosis of such patients and their response to treatment. Some reports have described permanent neurological impairment or death in diuretic-induced hyponatremia, while others have presented evidence of reversal of neurological manifestations and successful outcome with appropriate therapy. Thus, eight patients with severe hyponatremia (serum sodium level of 110 ±2 mmol/L) and overt neurological manifestations were treated with 3 percent sodium chloride solution. Within 28.8 ± 6 hours of treatment, the serum sodium level increased to 132 ± 5.6 mmol/L, indicating a correction rate of 0.87 ± 0.26 mmol/L per hour.

Seven of the 8 patients showed recovery of neurological manifestations and were discharged from the hospital. One patient died of an unrelated condition. Patients with this entity are usually old, often female, and underweight. Associated conditions, such as intractable diarrhea, tube feeding, hypoglycemic drugs, polydipsia, and cerebrovascular accidents may play a role in the pathogenesis of this condition.

Hyponatremia in Critically-Ill Neurological Patients

Hyponatremia is the most common and important electrolyte disorder encountered in the neurologic intensive care unit. Two main causes are: (1) SIADH, (2) cerebral salt wasting (CSW). Determination of the extracellular fluid volume remains the therapeutic endeavor between the two conditions. The differential diagnosis between these two diagnoses is presented in Table 2.

In essence, CSW represents primary natriuresis, leading to hypovolemia, sodium deficit, and low urinary sodium. Thus, treatment of CSW consists of sodium and water administration. Whereas, SIADH represents mildly volume overload state and treatment consists of fluid restriction. Details of management of these conditions will be found later. However, in the literature, there is abundant evidence to indicate that hyponatremia in intracranial disorders is mostly caused by CSW.

Hyponatremia in Severe Exercise or Among Marathon Runners

Hyponatremia occurs in a substantial portion of Marathon runners and can be severe. The single strongest predictor of hyponatremia in this situation is considerable weight gain during the race, which correlates with excessive fluid intake. Longer racing time and body mass index extremes are also associated with hyponatremia.

Hyponatremic runners have found to consume significantly more fluid than normonatremic runners, and female runners have consumed more fluid in proportion to body weight compared with male runners. In both symptomatic and asymptomatic runners, women develop

Table 2. Differential diagnosis of CSW and SIADH

Variable	*CSW*	*SIADH*
Extracellular fluid volume	↓	↑
Body weight	↓	↑
Fluid balance	negative	positive
Urine volume	↔ or ↑	↓
Tachycardia	yes	no
Hematocrit	↑	unchanged
Albumin	↑	unchanged
Blood urea nitrogen	high	low
Serum uric acid	high	low
Urinary sodium	high to low	high
Sodium balance	negative	negative or +
Central venous pressure	low (6 cm H_2O)	normal or slightly ↑ (6-10 cm H_2O)

hyponatremia more frequently than men. However, there is no evidence that asymptomatic hyponatremic female runners retain more fluid than hyponatremic male runners. The sodium supplementation trial, conducted during the 2002 Houston Marathon, confirmed that sodium supplementation had no protective effect on serum sodium levels in those runners who drank excessively. In a cohort of 33 runners, hyponatremia developed secondary to fluid overload, and additional sodium content resulted in fluid retention. This increased fluid retention would be detrimental if pulmonary edema and encephalopathy developed, suggesting that sodium supplementation might have harmful than beneficial effects in the development of fluid overload hyponatremia.

SYMPTOMS AND SIGNS OF HYPONATREMIA

Most cases of hyponatremia are usually asymptomatic and generally detected in the laboratory studies. A common cause of hyponatremia is pseudohyponatremia, which is commonly seen in association with hyperglycemia. Increase of glucose by 100 mg/dL above normal level decreases serum sodium by 1.6 mmol/L. Thus, in diabetic patients with glucose levels in the range of 300 to 400 mg/dL, low serum sodium is common. Reduction of glucose levels with insulin treatment is associated with concomitant increase of serum sodium.

On the other hand, hyponatremia can be mildly to severely symptomatic. Most common symptoms in hospitalized hyponatremic patients are confusion, disorientation, apathy, extreme weakness, anorexia, nausea, and vomiting. In a small but undefined percentage of patients with hyponatremia, symptoms can be more severe and are those of central nervous system disorder, such as tonic-clonic convulsion, respiratory arrest, or coma. Acute symptomatic hyponatremia may be seen in the following conditions:

1. SIADH
2. Compulsive water drinkers (water intoxication)
3. Postoperative hyponatremia
4. Overzealous use of potent diuretics
5. Acute alcoholism
6. Marathon runners
7. Drugs (Hydrochlorothiazide, chlorpropamide, fluoxetine). Hydrochlorothiazide is the most notable cause of hyponatremia in elderly thin females.

SIADH (Syndrome of Inappropriate Antidiureti Hormone)

SIADH is not a specific disorder but a phenomeno due to unregulated release of AVP from hypothalamu or release of vasopressin from sources other tha hypothalamus, such as underlying malignancy. Th release of AVP is largely controlled by osmoreceptor or plasma osmolality. Thus, 2 percent increase o decrease of plasma osmolality from normal level wil alter osmoreceptors signal and enhance or blunt releas of AVP, respectively. Through urinary concentration o dilution, the kidneys conserve or excrete water load respectively, thereby helping to maintain volum homeostasis. Inability to excrete free water may occu as a result of ineffective suppression of AVP, less solut intake, "reset osmostat," thus releasing AVP at a lowe level of osmolality or releasing AVP from sources othe than hypothalamo-pituitary axis. Besides osmoreceptors AVP release is also controlled to a small extent by caroti sinus baroreceptors that are activated by reduction o effective circulating blood volume. Administration o blood or fluid to restore circulating volume attenuate the signaling from carotid sinus baroreceptors t hypothalamus, thereby permitting normal or enhance water excretion. On the other hand, decreased effectiv circulating blood volume, as in congestive heart failur or cirrhosis of liver, may be a factor in high circulatin AVP with enhanced free water absorption and dilutiona hyponatremia. A patient is presented here to illustrat SIADH.

A 77-year-old white male was referred to the author o October 17, 2005, for low serum sodium (123 mEq/L). Hi main complaints were extreme weakness and tiredness, n appetite, and sleepiness all the time. He was taking low sal diet since August 2005. He was also severely hypothyroi his TSH on November 10, 2005, was 45 munit/L. He wa treated with 200 mcg of Synthroid® daily. Other medicatio consisted of furosemide 10 mg p.o. daily, Plavix® 75 m p.o. daily, potassium chloride 8 mEq p.o. daily, an Lipitor® 20 mg p.o. daily. On September 5, 2005, a seru chemistry showed sodium 123 mmol/L, potassium 4. mmol/L, chloride 94 mmol/L, CO_2 24 mmol/L, BUN 1 mg/dL, and serum creatinine 0.9 mg/dL. Prior to tha on August 26, 2005, his serum sodium was 130 mmol/ During this visit, furosemide was discontinued, an laboratory studies were ordered. He was also placed o salt tablet (1 g) two tablets three times daily. His seri

Table 3. Patient's serial serum chemistry and urine electrolytes and osmolality

2005	*Oct 17*	*Therapy*	*Oct 24*	*Therapy*	*Nov 5*	*Therapy*	*Nov 10*	*Nov 28*	*Dec 14*
Na mmol/L	123	salt	134	demeclocycline	137	demeclocycline	133	133	136
K mmol/L	4.5	tablet	4.4	300 mg PO	4.2	d/c due to	4.0	4.0	3.8
Cl	91	plus	99	twice daily	104	elevated	100	101	99
CO_2 mmol/L	27	fluid	26		27	liver enzymes	30	26	32
BUN mg/dL	29	restriction	19		16	salt tablet plus	13	15	25
Creatinine mg/dL	0.7		0.8		0.8	fluid restriction	0.8	0.9	1.0
Uric acid mg/dL	1.6		1.5		NA		2.2	2.6	4.9
URINE									
Na mmol/L	50		132						
Cl mmol/L	74		170						
K mmol/L	57		66						
Osmolality mOsm/kg	727		771						

Na = sodium; K = potassium; Cl = chloride; CO_2 = bicarbonate; BUN = blood urea nitrogen; PO = by mouth; NA = not available; d/c = discontinued

serum chemistry and urine electrolytes and osmolality are shown in Table 3.

Hyponatremia accompanied by low BUN and low serum creatinine levels indicates hemodilution caused by mild to moderate increase of extracellular volume. Low serum uric acid, a common accompaniment of hyponatremia, is due to enhanced urinary excretion of uric acid and is caused by increased extracellular volume. Other evidence of volume excess is increased urinary excretion of sodium and chloride as on October 24. His urinary osmolality (727,771 mOsm/kg) was elevated out of proportion to serum sodium or serum osmolality. His calculated serum osmolality on October 17, 2005, was 123 x 2 + 10 = 256 mOsm/kg, and on October 24, 2005, it was 134 x 2 + 10 = 278 mOsm/kg. With these serum hypoosmolalities, AVP release from hypothalamus is expected to be blunted, resulting in excretion of hypotonic urine (urine osmolality less than 100 mOsm/kg). But his urine was very concentrated with urine osmolality over 700 mOsm/kg, indicating an intact urinary concentration mechanism despite hemodilution. Thus, a diagnosis of SIADH was tenable with a conglomerate of:

1. Hyponatremia
2. Serum hypoosmolality
3. High urinary osmolality out of proportion to serum osmolality
4. Low BUN and serum creatinine levels
5. Very low serum uric acid with increase in uric acid level after total fluid restriction to 1 liter per day. As fluid restriction continued, his serum uric acid increased from 1.5 to 4.9 mg/dL.

The fact that patient felt well and had more energy than before is commensurate with increase of serum sodium. He was also eating well. He has had recurrent pleural effusion on the right side of his chest, requiring repeated thoracentesis for removal of fluid. Fluid cytology did not reveal malignant cells. Pleural biopsy study also was negative for malignancy.

As stated earlier, inability to excrete free water is the hallmark of SIADH. Inability to excrete free water is the result of uncontrolled release of AVP, as in postsurgery state or release of vasopressin from nonhypothalamic source, such as malignancy resulting in dilutional hyponatremia. Water loading test is designed to determine the kidney's ability to excrete free water and elucidate the pathogenesis of dilutional hyponatremia.

Water Loading Test

The test is conducted in the morning according to the following procedure:

1. A control-collection of urine is taken, and blood samples are drawn.
2. Urinary sodium and osmolality are measured, and blood samples are analyzed for sodium and osmolality.

Table 4. 80 kg white male water loading test

Control Hour	*Urine Volume (ml)*	*Urine Sodium (mEq/L)*	*Urine Osmolality (mOsm/kg)*	*Serum Sodium (mEq/L)*	*Serum Osmolality (mOsm/kg)*
1	water load (20 mL/kg) to drink	39	401	139	293
1	0				
2	260	61	431		
3	0				
4	0				
5	150	58	428	134	284

3. A standard water load consisting of 20 mL/kg per body weight is given to the patient to drink within 15 to 20 minutes.
4. Urine collection begins every hour for 4 hours (although the test can be extended to 5 hours). Vigilant attention must be paid to the patient to ensure that the patient doesn't drink additional fluid, which could lead to cerebral edema.
5. After 4 (or 5) hours, the total urine volume is measured, and the urine sample is analyzed for sodium and osmolality.
6. At the final hour, blood samples are again drawn and analyzed for sodium and osmolality.

The normal response with water load is a decrease in serum osmolality, resulting in a blunted signal to the hypothalamus, with slight or no release of AVP. Therefore, passage of a large volume of dilute urine is the characteristic normal response. After giving water load to a subject who is in normal fluid-electrolyte balance, serum osmolality will decrease; urine osmolality will decrease to less than 100 mOsm/kg and the result is excretion of the water load in 4 hours. The results of water loading test in a patient with SIADH are shown in Table 4.

He drank 1600 ml of water but excreted only 410 ml of urine in 5 hours. Thus, he retained 1190 ml of water, which is enough to give rise to hyponatremia and serum hypoosmolality. From Table 4, it should be noted that his serum osmolality decreased from 293 to 284 mOsm/kg (3.1 percent decrease of serum osmolality with expected blunting of release of hypothalamic vasopressin). Despite that, his urine osmolality increased from 401 to 428 mOsm/kg in 5 hours, which suggests an intact urinary concentrating mechanism and is due to release of vasopressin from hypothalamus at a low osmolar level, called "reset osmostat." Alternatively, vasopressin may be released from a source other than hypothalamus and independent of osmoreceptors signals. In this patient, vasopressin release was most likely from a malignant condition. This patient was later found to have a metastatic liver cancer.

Postsurgery Hyponatremia

Postoperative hyponatremia complicated by seizure, respiratory arrest, hypoxia, and death are mostly reported in women. The incidence of neurologic complications and mortality—with comparable degree of postoperative hyponatremia—is much lower in men compared to that in women, especially when compared with menstruating women. While about 1 percent of postoperative patients become symptomatic (hyponatremic encephalopathy), all postoperative patients are at a risk for the development of hyponatremia. The following types of surgery are commonly associated with hyponatremia:

1. Transphenoidal (TS) surgery for pituitary adenoma—most common
2. Other types of intracranial surgery
3. Adult spinal fusion surgery
4. Transurethral resection of prostrate
5. Endometrial ablation or hysterectomy
6. Labyrinthectomy

Table 5. Distinguishing features between different types of postoperative hyponatremia

TS-Hyponatremia	*Postsurgery Hyponatremia*
• It is not iatrogenic.	Frequently iatrogenic
• Inappropriate secretion of ADH is the mechanism of hyponatremia.	Induced by hypotonic fluid infusion (5% dextrose in water or ½ normal saline).
• Delayed onset (one week)	Rapid onset (36-46 h)
• Fluid restriction is appropriate treatment.	Hypertonic (3%) saline is the treatment of choice
• No morbidity or mortality.	High morbidity or mortality

7. Abdominal surgery, such as cholecystectomy

Hyponatremia following TS for pituitary tumors shows certain characteristic features. These are:

1. Develop most commonly in patients operated on for Cushing's disease.
2. Delayed appearance of symptoms, usually on the sixth or seventh postoperative day.
3. More common in women than men.
4. More common in menstruating women than menopausal women.

Menopausal women taking estrogen therapy are similarly vulnerable to hyponatremia as menstruating women. There are some differences between TS-associated hyponatremia and other acute postoperative hyponatremia, as shown in Table 5.

The most important and easily preventable risk factor in postoperative hyponatremia is administration of hypotonic fluids (0.45 percent saline or 5 percent dextrose in water). Intravenous hypotonic fluid should essentially be avoided in a postoperative patient. In summary, increased risk factors for neurologic complications of hyponatremia include:

1. Postoperative menstruant women
2. Elderly women on thiazide diuretic
3. Children
4. Alcoholic patients
5. Psychiatric polydipsic patients
6. Hypoxemia
7. Hypokalemia

Among the psychotropic drugs, fluoxetine (Prozac®) was associated with the most cases of acute hyponatremia. The median time of onset of hyponatremia was 13 days (range 3 to 120 days), three fourths of the cases presented within 30 days of initiation of therapy with this agent. The presentation was similar to that of SIADH.

Hyponatremia in Cerebral Malaria

Falciparum malaria can be associated with inappropriate secretion of ADH. Serum sodium was low in 13 of 17 patients admitted with a diagnosis of severe falciparum malaria. Serum sodium returned to normal levels during antiparasitic therapy. Urine sodium was high and serum osmolality was low consistent with SIADH in 6 out of 13 patients. ADH levels were inappropriately high in 6 patients, which confirm a diagnosis of SIADH. In another study, hyponatremia was observed in 52.6 percent of 19 children with cerebral malaria upon admission to a hospital. Another 1 percent developed hyponatremia between 48 and 96 hours after admission to hospital. Serum sodium ranged from 117 to 120 mmol/L. In 50 percent of these children, urinary sodium excretion was high. A significant negative correlation was obtained between hyponatremia and parasite density and between parasite density and urinary sodium excretion during the first 24 hours of hospital admission. Increase in plasma sodium in the first 24 hours of admission was associated with a reduction in seizure frequency compared with number of seizures prior to hospital admission.

Pathophysiology of Hyponatremia

The symptoms and signs of hyponatremia, especially those pertaining to central nervous system, mainly develop as a result of plasma hypoosmolality and shifting of free water from extracellular space to intracellular space. Brain is the most vulnerable organ affected in this fluid shifting process. Brain becomes edematous as a result of rapid shift of fluid from extracellular space to intracellular space in an osmotic gradient. Rapid development of hyponatremia is more likely to cause swelling of the brain than slow development of hyponatremia and, consequently, slow rate of fluid shift. Osmotic swelling of the brain is maximal in the first few hours of hyponatremia and is commensurate with the appearance of neurologic symptoms and signs. Gradually the brain adapts to its hyponatremic swelling process by generating solutes, which apparently help in the dissipation of the swelling. Pathologic examination of the brain from patients who died shortly after the onset of acute hyponatremia showed cerebral edema and brainstem herniation. However, the pathogenesis of dramatic and frequently catastrophic clinical consequences of acute hyponatremia, culminating in seizures, and respiratory arrest is still somewhat controversial. It is most likely related to rate of development of hyponatremia. Thus, with the same level of low serum sodium, some patients are symptomatic; some are not. Therefore, symptoms are related to the rate of development of hyponatremia. Hypoxia and hypokalemia are other factors that predispose to neurologic damage caused by hyponatremia.

A classical description of acute symptomatic hyponatremia associated with brain swelling was reported by Helwig and colleagues in 1935. They described the first case of fatal water intoxication resulting from the administration of large quantities of tap water by proctolysis. At autopsy, the brain was found to be uniformly enlarged, the ventricles reduced in size, the cerebral gyri flattened, and the subarachnoid space obliterated. This observation stimulated the investigators to design experiments in animals to reproduce the clinical and pathological features that were found in the patient as well as to study the chemical alterations in the tissues with the administration of tap water into the rectum of rabbits.

The problem of water intoxication was subsequently recognized, which facilitated recovery of the subsequent patient by the administration of hypertonic salt solution. The first report was in a 64-year-old woman who entered the hospital because of vaginal hemorrhage and fatigue. Admission blood pressures were 144 mm systolic and 80 mm diastolic, pulse 80/min and regular. Serum chemistry was not done on admission. The following day, the patient was taken to the operating room, her abdomen was opened, and a large myoma of the right broad ligament was found. A panhysterectomy and appendectomy were performed. In the recovery room, a proctolysis of tap water was started. About 36 hours after surgery, when she had absorbed approximately 7 liters of water, she became comatose and developed convulsions. She became cyanotic and exhibited Cheyne-Stokes respiration and a bilateral Babinski's sign. She received a total of 8,250 ml tap water per rectum. Administration of 5 percent sodium chloride solution resulted in prompt arousal of the patient and gradual disappearance of all the symptoms and signs. Two weeks after discharge from hospital, she showed normal physical and mental function. Since then, a few autopsy studies were done in patients with acute hyponatremia and, in some cases, brain stem herniation was noted, which was considered to be the cause of death.

SUMMARY OF DIAGNOSIS OF HYPONATREMIA

1. Inability to excrete free water is probably the most common cause of acute and symptomatic hyponatremia. Associated conditions include SIADH, compulsive water drinking as seen in psychiatric units, a postsurgical state, and the use of some drugs.
2. Diuretics, especially hydrochlorothiazide, fluoxetine, tricyclics antidepressants, and calcium antagonists, are all associated with development of hyponatremia.
3. Hyponatremia is common in postsurgical patients, particularly in those who have been operated on trans-sphenoidally for pituitary tumors.
4. The most common cause of hyponatremia in postsurgical patients is infusion of hypotonic fluid (5 percent dextrose or ½ normal saline).
5. All hyponatremic states have in common elevation of plasma vasopressin levels.
6. Signs and symptoms of hyponatremia are uncommon, unless the serum sodium concentration has decreased to or below 125 mmol/L and has reached this level at a rapid rate (in less than 24 hours).
7. A slow decrease of the serum sodium concentration to even a very low level (110 mmol/L) may give rise to no or mild symptoms (i.e., apathy, anorexia), whereas a decrease of even 5 to 6 mmol/L from the baseline at a rapid rate is likely to result in central nervous system symptoms.
8. Hyponatremia is an important cause of seizure in infants younger than 6 months.
9. The presence of signs and symptoms of hyponatremia is the sole determining factor for the type of treatment and rapidity of initiation of treatment.

Treatment

Old Adage—

"Hyponatremia that develops fast should be treated fast; whereas hyponatremia that develops slowly should be corrected at a proportionately slower pace". Likewise, evolution as well as severity of the symptoms and signs of hyponatremia are directly proportional to the rate of development of hyponatremia. Hence, a patient is most likely to be very symptomatic, if serum sodium decreases rapidly in a matter of hours, such as water intoxication. On the other hand, a patient is unlikely to show severe symptoms or signs of hyponatremia, i serum sodium level drops slowly over a period of severa days. Therefore, the presence of symptoms and signs i the sole determining factors for the type of treatmen and the rapidity of initiation of treatment. Overall there is slight or no disagreement for an aggressiv treatment for symptomatic hyponatremia, whereas more conservative approach is generally recommende for asymptomatic hyponatremia. As vast majority o hyponatremic patients are asymptomatic or mildl symptomatic, total fluid restriction of 1 to 1.2 liters pe day is the treatment of choice. With fluid restriction, extracellular volume is contracted resulting in increase of serum sodium and serum osmolality. This treatment has a low compliance rate, however. Therefore, salt tablet 1 g two to three times daily is most frequently prescribed to increase serum sodium.

Acute Symptomatic Hyponatremia

A patient was brought to the emergency room for confusion, disorientation, and seizure activity. His serum Na^+ was 105 mEq/L. Most clinicians agree that such a patient will be treated with hypertonic saline (3 percent NaCl solution). The total volume of hypertonic saline and the ideal rate of its administration are not established. The following formula might help to determine the total volume of hypertonic saline needed (L) = $\Delta[Na^+]$ x total body water/$[Na^+]$ iv - $[Na^+]$s where $[Na^+]$ iv in the intravenous fluid and $[Na^+]$s the target serum $[Na^+]$. One liter of 3 percent saline contains 510 mEq/L of $[Na^+]$.

For example, if a patient with a serum $[Na^+]$ of 110 mmol/L has an estimated total body water of 40L, and the target serum $[Na^+]$ is 120 mmol/L to be achieved over a 24-hour period with 3 percent saline, the required volume of 3 percent saline will be calculated as follows: 10 x 40/510–120 = 1.025 L of 3 percent saline in 24 hours, which is 41.6 ml/h. However, in general, it is safe to administer 50 ml/hour to increase serum Na^+ by 1 mmol/L per hour up to 10 to 12 mmol/L total in the first 24 hours or until the neurological symptoms and signs have abated. Serum Na^+ should be monitored every 4 to 6 hours during infusion of hypertonic saline solution. Furosemide 1 mg/kg IV had been given to facilitate free water excretion. The author does not recommend that. It should be noted that 50 ml of hypertonic saline infusion will deliver 25.5 mmol/L of Na^+ per hour. Thus, the expected rise of serum Na^+ should be 1.56 mmol/L/hour in a person with 40L of total body water. In an asymptomatic hyponatremic patient, a combination therapy with total fluid restriction to 1 liter per day and salt tablet 1 g po bid or tid is commonly prescribed. There is some controversy among the nephrologists about the use of 3 percent saline in an asymptomatic hyponatremic patient. Some nephrologists will prescribe 3 percent saline in asymptomatic hyponatremia if serum Na is less than 120 mmol/L for fear of convulsions. Demeclocycline 300 to 600 mg po bid can be prescribed if fluid restriction and salt tablet fail to increase serum Na^+. Demeclocycline is an expensive drug; therefore, careful consideration should be given before prescribing this drug. Utmost attempt should be made to first try total fluid restriction and salt tablet before prescribing demeclocycline. Demeclocycline is a tetracycline derivative and is metabolized by the liver. Hence, liver function test should be obtained during the course of demeclocycline therapy. Should liver function test be abnormal, demeclocycline dosage is decreased or discontinued. Metabolites of demeclocycline are excreted by the kidney and may lead to nephrotoxicity. A patient is presented here to illustrate the effectiveness of combination therapy.

An 85-year-old white female was brought into the emergency room of a local hospital by her daughter on September 26, 2007, with complaint of extreme weakness of the lower extremities and feeling of tiredness. She has a history of hypertension and was taking hydrochlorothiazide 12.5 mg po daily. On initial examination, she was alert and oriented but gave history of slight headache and one episode of vomiting. Physical examination was essentially negative. Her admission and subsequent laboratory studies and treatment profile are presented in Table 6. Hydrochlorothiazide was discontinued in the emergency room. Her blood pressure was in the normal range.

Infusion of 3 percent sodium chloride solution for six hours further decreased serum Na^+. It was felt that this infusion is unlikely to increase her serum NA^+. Therefore, the infusion was discontinued, and she was placed on total fluid restriction to 1 liter total per day, salt tablet 1 g po TID and demeclocycline 600 mg po twice daily. From Table 6, her hyponatremia and hypokalemia both were due to hydrochlorothiazide. Elevated glucose was due to volume depletion. Interesting finding was the elevation of BUN from the time of admission, suggesting volume contraction associated with fluid restriction. When fluid restriction was slightly liberalized on September 29, her serum Na^+ decreased. Fluid restriction to 1 liter was reinstituted on September 30. On October 1, spironolactone was discontinued. On October 2, her serum Na^+ increased to 134 mEq/L. She was discharged from the hospital. Outpatient laboratory on October 8, 2007, showed serum Na^+ 138 mEq/L.

Isotonic saline has a limited therapeutic value in treatment of euvolemic hyponatremia, as in SIADH. Since these patients characteristically have high urinary sodium (Na) plus urinary potassium (K)

Table 6. Patient data of September 2007

September 26					27	28	29	30
Adm	6h		Midnight					
Na^+ (mmol/L)	116	3% NaCl solution infusion with 20 mEq KCl/at 50 ml/h started. Amiloride 5 mg po then 2.5 mg po BID started.	115	D/C 3% NaCl infusion. Fluid restriction to 1 liter per day, salt tablet 1g po tid demeclocycline 600 mg po BID started.	125	127	133*	131**
K^+ (mmol/L)	2.4		2.3		3.4	3.7	4.6±	4.5
Cl^- (mmol/L)	77		76		91	96	103	102
CO_2^- (mmol/L)	28		28		24	24	24	25
Glucose (mg/dL)	164		156		96	137	94	83
BUN (mg/dL)	9		8		17	22	20	18
Scr (mg/dL)	0.58		0.53		0.59	0.81	0.64	0.56
eGFR (ml/min)	>60		>60		>60	>60	>60	>60
Calcium (mg/dL)	8.1		8.4		8.0	8.0	7.8	7.9
Magnesium (mg/dL)	2.2		1.5		2.3	ND	NA	NA
Uric acid (mg/dL)	NA		NA		3.0	ND	NA	NA

* Fluid intake increased to 1500 ml/day.

** Spironolactone 25 mg po BID started for blood pressure control.

± Amiloride was discontinued. KCl intake was put on hold; then discontinued.

NA = not available; ND = not done; d/c = discontinued.

concentrations that exceed the plasma Na concentration, the administration of isotonic saline results in further worsening of hyponatremia. Because isotonic saline contains more water than [Na] sodium (90 mEq/L), for instance, 100 ml solution contains 9 mEq Na^+. This is particularly seen in postoperative patients characterized by elevated vasopressin levels, the so-called "desalination" phenomenon.

Overcorrection (more than 25 mmol/L on day 1) or rapid correction of hyponatremia is frequently refrained for fear of central pontine myelinolysis, but it has not been confirmed. In fact, the hazards of seizures, coma, and respiratory arrest clearly outweigh the risk of overcorrection or rapid rate of correction, which is done to result in complete reversal of the neurologic manifestations. The central pontine myelinolysis or necrosis is characterized by insidious onset of flaccid quadriplegia, cranial nerve abnormalities, manifesting as pseudobulbar palsy, and alteration in mental status, including behavioral changes. There is some consensus that absolute magnitude of correction, rather than the rate of correction, may increase the risk of this demyelination syndrome. Correction rates exceeding 2.5 mmol/L per hour, or an absolute increase of more than 25 mmol/L on day 1 or both, has been associated with a very high rate of demyelination. Evidence from studies in experimental animals is supportive of absol overcorrection more than the rapid rate of correction hyponatremia as a risk for demyelination syndrome. Al there is some consensus that correcting hyponatren of shorter duration (acute onset) carries no untowa consequences regardless of the treatment regime However, demyelinating lesions are more likely to occ in patients with chronic asymptomatic hyponatren or those with pre-existing other abnormalities, such chronic alcoholism, malnutrition, or chronic hypokalem Therefore, potassium of 20 to 40 mEq should be added a liter bag of hypertonic saline or be given orally to av hypokalemia and its adverse effect on brainstem.

Chronic or Recurrent Hyponatremia

Any one of the following regimens may be recommen for the treatment of chronic or recurrent hyponatrem

1. Water restriction of one liter/day.
2. Salt tablet 1 g per oral BID or TID + furosemide 40 per oral once or twice daily. Water restriction u 1 liter/day is very effective in increasing serum However, compliance remains a problem with wa restriction.
3. Since chronic or recurrent hyponatremia is comm in SIADH, demeclocycline is recommended inhibit the effect of vasopressin at the collect

tubules and induce nephrogenic diabetes insipidus. Demeclocycline is a tetracycline derivative, which may produce side effects consisting of phtophobia, malabsorption syndrome, and elevated liver enzymes. In patients with abnormal liver function, incidence of nephrotoxicity is higher than with normal liver function. Demeclocycline is prescribed as 300 to 600 mg po twice daily. In chronic user of demeclocycline, liver function tests should be evaluated regularly.

Vasopressin Antagonists

The AVP receptor antagonists, a new class of agents for the treatment of hyponatremia, are associated with few adverse effects and have distinct advantages over other agents, such as demeclocycline. AVP exerts its physiologic effects through V_1 or V_2 receptors. V_2 receptors are located in the cortical and medullary collecting tubules and activate aquaporins, resulting in reabsorption of free water.

Antagonists of AVP V_2 receptors induce water diuresis and are generally believed to have slight effect on solute excretion. There are several AVP receptor antagonists available, including conivaptan, lixivaptan, tolvaptan, and satavaptan. Conivaptan and tolvaptan are the ones approved by Food and Drug Administration (FDA) for use in the United States. Indications include euvolemic hyponatremia, such as SIADH or hyponatremia associated with congestive heart failure. The largest studies employing an AVP antagonist (tolvaptan) are SALT I and SALT II trials. At all time-points, serum Na was higher in tolvaptan-treated subjects and the effect was reversible. The mean increase in serum Na in SIADH was higher than that in congestive heart failure or cirrhosis of liver. It is expected that effect of conivaptan will be similar to tolvaptan.

Conivaptan is administered mixed in a 5 percent dextrose solution by bolus intravenous infusion of 20 mg over 30 minutes followed by continuous intravenous infusion of 20 to 40 mg over 24 hours. The increase in serum Na seen with conivaptan 40 and 80 mg/day is dose related and gradual over a 4-day period. Conivaptan is generally well tolerated. Because conivaptan has an aquaretic effect, a rapid rise in serum Na level (>12 mEq/L in 24 h) can result. Therefore, frequent monitoring of serum Na and volume status is essential. In those who develop rapid rise in serum Na, conivaptan will be discontinued and neurologic status be checked. The most common adverse reaction reported with conivaptan was infusion-site reactions, which may be attributed to the acidity of the solution that contains the drug (pH 3.0). However, most infusion-site reactions were mild and did not require discontinuation of treatment. Another reported adverse reaction was thirst, which is attributed to rapid increase in serum Na. Vomiting and hypokalemia may develop. It is important for the readers to know that this drug is not yet widely available and also very expensive.

Tolvaptan oral preparation is now available. Initial dose is 15 mg daily but may be increased to 60 mg daily. Correction rates seem to be similar among patients with congestive heart failure and SIADH but may be somewhat lower among patients with cirrhosis. In all patient subgroups, serum Na levels may decline by withholding tolvaptan for several days, indicating a need for continued tolvaptan therapy to maintain serum sodium normalization. The most common adverse effects attributed to tolvaptan therapy were kaliuresis, thirst, fatigue, dry mouth, polyuria (due to kaliuresis), and polydipsia (due to increase in serum Na^+).

Prevention

1. Hyponatremia is common in postsurgery patients, particularly when the surgery was done transsphenoidally for pituitary tumors. Hyponatremia is mild and takes 1 week to develop in patients who have undergone intracranial surgery. Fluid restriction alone could mitigate the development of hyponatremia in these patients.
2. Infusion of hypotonic fluids, such as 5 percent dextrose in water or 0.45 percent saline must be avoided in postsurgery or in trauma patients in whom the AVP level is high. The danger of development of severe symptomatic hyponatremia is quite high with use of hypotonic fluids.
3. Close monitoring of compulsive water drinkers, many of whom have psychiatric illness, is necessary to prevent water intoxication.
4. Correction of serum potassium levels, even before correction of serum sodium levels, could reduce the incidence of central pontine myelinolysis in hyponatremic patients.
5. Fluid restriction of 1 liter per day and salt tablet 1 g po BID or TID are effective prevention therapy.
6. Tolvaptan 15 to 60 mg po daily will be worth trying to keep serum Na^+ at a normal or near normal level.

KEY POINTS

1. Hyponatremia of variable severity is a common laboratory abnormality among hospitalized patients.
2. Hyponatremic patients may be asymptomatic, slightly symptomatic, or severely symptomatic. Neurologic symptoms and signs are considered alarming and warrant immediate and aggressive treatment.
3. Intravenous infusion of hypertonic (3 percent) saline is the treatment of choice in hyponatremic patients associated with neurologic manifestations.
4. Total fluid restriction and/or salt tablets are adequate in mildly symptomatic or recurrent hyponatremic patients. Demeclocycline may be tried in noncompliant patients with fluid restriction.
5. Temptation of treatment with infusion of hypertonic saline in asymptomatic chronic or recurrent hyponatremic patients should be discouraged. Such therapy carries a high risk of central pontine myelinolysis.
6. Infusion of AVP V2 receptor antagonist, conivaptan intravenously or preferably tolvaptan po, may be tried in recurrent hyponatremia.

Question and Answer Relative to Hyponatremia

62-year-old male with difficulties in concentrating and somewhat increasing somnolence was noted by wife. He gave history of coronary artery disease and hypertension. He was treated with metoprolol, lisinopril, simvastatin, and aspirin. He gave history of 20-pack-a-year smoking but no alcohol or substance abuse. Review of system: chronic cough, no weight loss, BP 134/86, mmHg with no orthostatic change, pulse 68/min, no edema, BMI 28, Na 123 mmol/L, K+ 4.0 mmol/L, chloride 93 mmol/L, CO_2 31 mmol/L, glucose 100 mg/dL, BUN 20 mg/dL, creatinine 0.9 mg/dL. What is the likely cause of this patient's hyponatremia?

• cirrhosis	5 percent
• heart failure	13 percent
• penal disease	8 percent
• ***SIADH***	69 ***percent***
• polydipsia	5 percent

Dilutional hyponatremia includes patients with heart failure, cirrhosis, and SIADH. They do not have a deficiency of body sodium; they have an excess of body water. In this patient, the absence of orthostatic changes or edema makes this a case of euvolemic hyponatremia for which SIADH is the most common cause. By the way, chronic cough is surely due to lisinopril.

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4

Hypernatremia: Pathophysiology, Diagnosis, and Management

Anil K Mandal

INTRODUCTION

Hypernatremia is a disorder of water metabolism and defined by the elevation of serum sodium (Na^+) higher than 145 mmol/L. Hypernatremia may be found as a laboratory abnormality in patients showing no symptoms or may be associated with a clinico-pathologic syndrome. If it remains untreated or is improperly treated, the disorder may lead to death in as many as 40 to 60 percent of patients. The condition primarily affects the central nervous system; in essence, a surplus of sodium in the extracellular space causes the brain to shrink, usually producing initial signs of altered mental state. The severity of cellular injury and development of symptoms is proportional to the rapidity and degree of fluid shift from intracellular space to extracellular space.

Disturbingly, hypernatremia occurs in about one to three percent of elderly persons (≥ 65 years) and in 0.3 to 1 percent of hospitalized patients. The effects of hypernatremia are reversible, however, only if action is taken promptly. Even more important, the condition is in great measure preventable, the only requirement being the availability of free water. Thus, familiarity with how hypernatremia occurs and with its signs and symptoms is extremely important.

ETIOLOGY

Hypernatremia may occur as a result of:

1. Water depletion in excess of sodium depletion, or
2. Sodium gain in excess of water gain.
3. Water depletion may occur in the form of either pure water loss or of hypotonic fluid loss. Thus, hypernatremia may be associated with normovolemia, hypovolemia, or hypervolemia. Accordingly, the causes of hypernatremia are divided into the following categories:

Category A: Hypernatremia associated with hypovolemia.

This may occur in conditions in which there is a profound loss of hypotonic fluid (loss of both sodium and water, with slightly more water than sodium).

Examples

1. Hyperglycemic hyperosmolar nonketotic coma
2. Tube feeding of high osmolar fluid
3. Hot-humid weather
4. Gastroenteritis
5. Peritoneal dialysis with hypertonic (4.25 percent) dextrose solution
6. Use of osmotic diuretic, such as mannitol
7. Postobstructive diuresis
8. Febrile conditions (excessive insensible perspiration).
9. Diuretic phase of acute tubular necrosis.

Category B: Hypernatremia associated with normovolemia (usually mostly free water loss)

Examples:

1. Central diabetes insipidus
2. Nephrogenic diabetes insipidus
3. Psychogenic polydipsia

In these conditions, hypernatremia generally does not occur unless thirst mechanism is impaired; patient is confused, febrile or has no access to free water.

Category C: Hypernatremia associated with hypervolemia.

Examples:

1. Excessive intake of $NaHCO_2$
2. Excessive infusion of normal saline
3. Infusion of hypertonic saline
4. Drowning in salt water ocean

Risk Factors for Hypernatremia

- Age over 65 years
- Mental or physical disability and inadequate support system
- Residence in nursing home
- Hospitalization and have intubation
- Impaired cognitive function
- Urine concentrating defect (diabetes insipidus)
- Solute diuresis (diabetes mellitus)
- Obstructive uropathy
- Recovery phase of acute tubular necrosis

Hypernatremia and Aging

The attenuated physiologic responses associated with aging certainly increase the overall risk of hypernatremia in elderly persons. Among the responses blunted by aging is the response to exogenous vasopressin; older people tend to have inadequate urine concentration, predisposing them to hypernatremia. In addition, levels of vasopressin in older persons may be inappropriately low in relation to plasma osmolality. Not all elderly patients will have equal risk, however. The condition is more likely to occur in nursing home patients and in those whose access to free water is limited by disability and inadequate support system. Hospitalization and intubation are associated with increased risk because they themselves are associated with greater disability and physical limitations on fluid intake.

Other Risk Factors

Additional risks for hypernatremia are directly related to the pathogenic mechanisms including a preexisting urinary concentrating defect, such as diabetes insipidus, previous diuretic therapy; the presence of solute diuresis caused by such conditions as uncontrolled diabetes mellitus; and obstructive uropathy after catheterization. The risk of hypernatremia is especially high in patients in whom an acute febrile illness or cognitive impairment has developed during hospitalization. Elderly individuals don't drink as much as young individuals. The decreased fluid intake in elderly persons has been attributed to impaired thirst. The exact mechanism of the decreased thirst sensation is undetermined. However, it may be related to low vasopressin secretion in elderly persons. This idea is not well founded as patients with central diabetes insipidus don't develop hypernatremia unless their thirst sensation is impaired or they have no access to water, such as living or traveling in deserts.

PATHOPHYSIOLOGY

In the preceding chapter on hyponatremia, it has been stated that serum Na^+ largely reflects the state of body water. Therefore, changes in body water, high or low is reflected upon the serum Na^+ concentration. When body water level rises, serum Na^+ level tends to decrease; whereas when body water level decreases, serum Na^+ level is likely to increase. In case of loss of body water, initially extracellular fluid (ECF) space becomes contracted and hypertonic, then the intracellular fluid (ICF) space with two thirds of body water tries to minimize ECF space hypertonicity by allowing shifting of water from the intracellular space to the extracellular space. In so doing, and if fluid shift continues, eventually the ICF space shrinks. Meanwhile plasma becomes hypertonic with increase in osmolality and viscosity All these may compromise microcirculatory blood flow

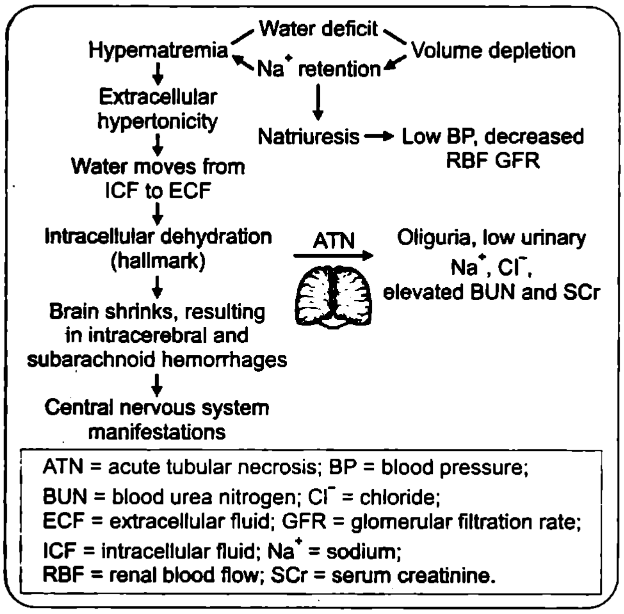
Intracellular dehydration is the hallmark of severe hypernatremia and is the major determining factor fo the pathophysiology, symptomatology and prognosi of hypernatremia. This is depicted in Figure 1. Brain i the target organ of involvement, but other solid organs such as kidney and the liver may also be involved i hypernatremic dehydration. Intracellular dehydratio accompanied by capillary ischemia frequentl culminates in cellular necrosis and hemorrhage. Cellula necrosis and hemorrhage in different organs gives ris to variable symptoms and signs. However, the mos predominant symptoms are those of cellular dehydratio and hemorrhage in brain. Cells in a dehydrated brai contract, producing traction on capillaries resulting i intracerebral or subarachnoid hemorrhages. In additio intracranial pressure decreases acutely as neuronal cel shrink, leading to herniation of brain stem. During th first week of hypernatremia, the water content of th brain will decrease by approximately 10 percent. A adaptation process restores 98 to 99 percent of the initi volume, however. The protective mechanism with the brain includes an increase of solute, composed of potassium, sodium, and chloride, and of amino acids and unidentified, or idiogenic osmoles. Idiogenic osmoles begin to accumulate about an hour after the onset of hypernatremia; the level stabilizes within days, after which the osmoles persist for another week or so, protecting the brain from further dehydration.

The mechanism just described may become a liability if the correction of hypernatremia is not carefully calculated. Brain edema may occur leading to convulsions, if sodium levels are reduced more rapidly than the idiogenic osmoles are able to dissipate.

In the kidneys, diminished renal blood flow and a decreased glomerular filtration rate will lead to reversible acute renal failure. Without treatment, subsequently acute tubular necrosis may develop, resulting in progressive renal failure.

Clinical Manifestations

The severity of clinical presentation varies depending upon the degree and duration of the fluid loss. Typically severe hypernatremic dehydration is seen in an elderly nursing home residents who are also disabled from stroke, amputation or fracture. They are more commonly males than females. Most commonly they are unresponsive or minimally responsive to painful stimuli, emaciated and dry. Their skin turgor is poor. They are often febrile, and almost invariably have low blood pressure and small urine volume. Abnormal speech (which may be due to previous stroke or extreme dehydration) is common. Myoclonic jerks (which may be due to severe azotemia) are not uncommon. However, tonic and clonic convulsions (grand mal seizures) are uncommon.


Hypernatremia
Water deficit
Volume depletion
Na⁺ retention
Extracellular hypertonicity
Natriuresis
Low BP, decreased RBF GFR
Water moves from ICF to ECF
Intracellular dehydration (hallmark)
ATN
Oliguria, low urinary Na⁺, Cl⁻, elevated BUN and SCr
Brain shrinks, resulting in intracerebral and subarachnoid hemorrhages
Central nervous system manifestations

ATN = acute tubular necrosis; BP = blood pressure;
BUN = blood urea nitrogen; Cl⁻ = chloride;
ECF = extracellular fluid; GFR = glomerular filtration rate;
ICF = intracellular fluid; Na⁺ = sodium;
RBF = renal blood flow; SCr = serum creatinine.

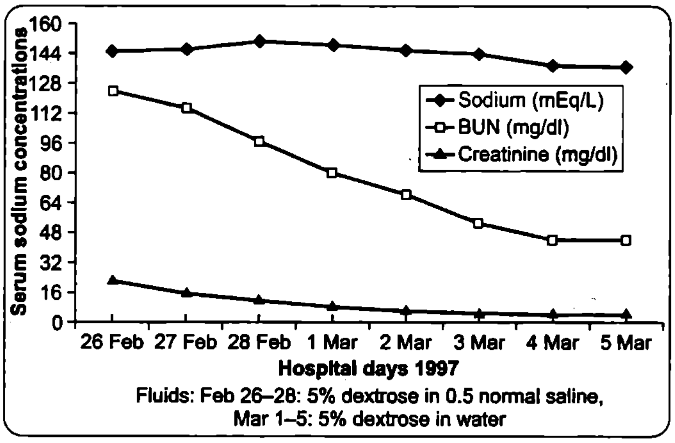
Figure 1: Pathophysiology of hypernatremia

Hospital-acquired Hypernatremia

Hypernatremia is increasingly recognized among the hospitalized patients. Most commonly, they are in the intensive care units and are critically ill. In our study hypernatremia was detected in 95 percent of the nonsurvivors in the hospital. This incidence is fairly similar to that in other studies. The etiology of hospital-acquired hypernatremia is unclear. However, our observation indicates that hospital-acquired hypernatremia is due to continuous infusion of normal saline in critically ill patients and their inability to excrete sodium for the underlying critical illnesses. However, except for altered mental status these patients are not nearly as symptomatic as those who are hypernatremic upon admission. Mental state worsens with continuous or repeated infusion of normal saline or half normal saline. Several patients are presented here to exemplify hospital-acquired hypernatremia.

Patient #1

An extraordinary case of hospital-acquired hypernatremia is illustrated in Figure 2. Initially, serum sodium was normal but increased with 5 percent dextrose in 0.5



Fluids: Feb 26–28: 5% dextrose in 0.5 normal saline, Mar 1–5: 5% dextrose in water

Figure 2: Renal function and electrolyte trends in patient #1

normal saline infusion. BUN and serum creatinine decreased. However, after changing infusion to 5 percent dextrose in water only, serum sodium returned to normal and renal function steadily improved.

Patient #2

A 72-year-old African-American male, nursing home patient with previous diagnosis of diabetes mellitus, alcoholic cirrhosis of liver, peripheral vascular disease with bilateral below knee amputation, cerebrovascular accident and prostatic cancer was admitted to acute care facility in a local hospital in Dayton, Ohio on March 31, 1991, with a history of fever, decreased oral fluid intake and confusion for two days. He was febrile with temperature ranging from 100 to 101°F, and a pulse rate of 120/min, but regular. Blood pressure was 140/70 mmHg in supine position. However, standing blood pressure could not be obtained. Upon admission, impaired swallowing was noted. A chest X-ray showed features suggestive of aspiration pneumonia of the right lung.

A complete blood count showed hemoglobin 9.9 g/dL, WBC 8.9 x 10^3/cmm, platelets 97,000 per cmm. Renal function test (BUN, serum creatinine), serum electrolytes and glucose upon admission and thereafter are presented in Table 1.

Initial treatment consisted of normal saline infusion at a rate of 100 ml/hour and antibiotics. Normal saline infusion was started with the idea to improve extracellular volume. However, as seen in Table 1, hypernatremia got worse and mental state deteriorated further. Glucose control improved but renal function remained low. Because of worsening hypernatremia and concomitantly deteriorating mental state, normal saline infusion was discontinued and infusion of 5 percent dextrose in water was begun. Regular insulin on a sliding scale was used to control hyperglycemia. As shown in Table 1 dextrose infusion made his serum sodium and renal function to return to normal levels. He became alert and oriented. It should also be noted that dehydration causes or aggravates hyperglycemia due to blunted insulin release and was evident in this patient. His blood glucose increased to 582 mg/dl upon admission, but decreased to baseline levels upon normal saline administration. Hypernatremia in this patient was probably the result of prolonged deficiency o oral fluid intake due to stroke and debilitated condition This was further aggravated by the febrile condition wit excessive insensible perspiration and loss of hypotoni fluid. Postural change in blood pressure was unobtainable but diminished renal function suggested hypovolemi state. In our experience, normal saline or even 0.45 percen saline worsens hypernatremia as observed in this patien On the other hand, dextrose solution provides free wate as dextrose is oxidized. Hence, free water loss is replete and serum sodium level decreases steadily toward norma In hypernatremic patients, any further free water los must be avoided. Free water loss through glucosuria i uncontrolled diabetes mellitus is an example. Therefor tight glycemic control with adequate doses of insuli (both short- and long-acting insulin) is essential in hypernatremic patient who has diabetes mellitus an or is treated with 5 percent dextrose solution. Similarl any agent, which may cause loss of more free water th sodium such as loop acting diuretic, must be avoided. patient is exemplified to that effect.

Table 1. Admission and follow up of serum electrolytes, glucose and renal function test

1991 March-April	*31*	*01*	*02*	*03*	*04*	*05*
Na^+ (mmol/L)	153	151	165	158	151	145
K^+ (mmol/L)	4.6	4.5	4.3	3.7	3.5	3.2
Cl^- (mmol/L)	111	114	124	118	112	105
HCO_3^- (mmol/L)	29	30	27	27	22	26
Glucose (mg/dL)	582	341	251	473	379	236
BUN (mg/dL)	56	60	60	42	32	18
Serum Creatinine (mg/dL)	2.0	2.1	2.0	1.6	1.5	1.3
	Infusion of Normal Saline			Infusion of 5 percent Dextrose in Water		

Patient #3

A 94-year-old white male was transferred from community hospital in Chillicothe, Ohio, to a tertiary ca hospital in Dayton, Ohio, for elevated BUN and seru creatinine levels and a need of dialysis treatment. admission, he was alert but lethargic. He was sever anemic. His hemoglobin and hematocrit were 6.4 g/ and 20.9 percent, respectively. His white blood cell co was normal. His admission serum chemistry was B 110 mg/dL, creatinine 6.8 mg/dL, sodium 148 mmol potassium 3.3 mmol/L, chloride 119 mmol/L, a bicarbonate (as CO_2) 12 mmol/L. Admission and serial serum chemistry are presented in Table 2.

He was transfused with two units of packed red blood cells, which promptly increased his hemoglobin and hematocrit to 14.9 g/dL and 43.9 percent, respectively. These levels remained unchanged or increased during the hospital course. He was infused with normal or half normal saline; thereafter, serum sodium and chloride progressively increased. On his third hospital day, his serum sodium and chloride levels were 156 mmol/L and 127 mmol/L, respectively. An unidentified doctor thought that patient had fluid overload and gave him an intravenous bolus of furosemide 40 mg. On day 5, his serum sodium and chloride levels increased to 165 mmol/L and 135 mmol/L, respectively. He became unresponsive and died. This patient clearly illustrates that loss of free water induced by furosemide in a hypernatremic patient enhanced rapid elevation of serum sodium from 156 to 165 mmol/L. Clearly, in hypernatremic patient, free water loss must be avoided or replaced quickly.

Table 2. Admission and follow up of renal function and serum electrolytes

Laboratory serum chemistry	*Admission*	*Day 2*	*Day 3*	*Day 5*
BUN (mg/dL)	110	108	90	48
Creatinine (mg/dL)	6.8	6.2	4.4	1.7
Sodium (mmol/L)	148	150	156	165
Potassium (mmol/L)	3.3	3.8	4.0	4.3
Chloride (mmol/L)	119	121	127	135
Bicarbonate (mmol/L)	12	10	11	14

Patient #4

GD an 87-year-old white male and nursing home resident was admitted to the hospital on June 7, 2010, with a diagnosis of change in mental status. He was treated with infusion of normal saline at 100 ml/h from June 7 through June 8 and then changed to 5 percent dextrose in water from June 9. He also received free water 200 ml every 4 hours through nasogastric tube and aqueous Pitressin• 5 units subcutaneously every 12 hours for 48 hours. His hospital course is shown in Table 3.

Laboratory Studies

Routine blood count and chemistry typically show elevated hemoglobin and hematocrit, variably elevated blood urea nitrogen, and mildly elevated serum creatinine levels, all of these are indicative of overall severe dehydration. Variably elevated uric acid is common due to dehydration (will find later). Serum sodium is elevated ranging from 151 to 170 mEq/L or higher and is accompanied by proportionately elevated serum osmolality. Serum potassium can be low, normal, or high. Serum chloride is elevated in proportion to serum sodium. Carbon dioxide is often reduced and consistent with simple metabolic acidosis or mixed metabolic acidosis and respiratory alkalosis. Urinary infection is common from debilitation or indwelling catheter and a source for fever and positive blood culture.

Table 3. Hospital-acquired hypernatremia

Laboratory Chemistry Panel	*June 7 on admission*	*June 7 after infusion*	*June 9 after 2nd infusion*	*June 12**	*June 21***
Na (mmol/L)	156	158	161	145	152
K (mmol/L)	3.6	3.4	6.2	3.3	3.3
Cl (mmol/L)	117	121	130	110	117
CO_2 (mmol/L)	30	29	28	27	28
ΔGlucose (mg/dL)	156	136	111	76	170
BUN (mg/dL)	46	45	37	9	29
Cr (mg/dL)	1.10	0.96	0.97	0.56	0.93
eGFR (ml/min)	>60	>60	>60	>60	>60

* Improved slightly; stayed in hospital.

** Restarted normal saline infusion on June 18, serum Na increased, and patient became unresponsive

MANAGEMENT OF HYPERNATREMIA

The treatment for hypernatremia is free water. The rate of administration of free water will depend upon the severity of symptoms of hypernatremia. The same principle will apply here as in hyponatremia. Thus, severely symptomatic patients warrant rapid fluid therapy; whereas in mildly symptomatic patients hypernatremia should be corrected at a much slower rate. Therefore, if patient is alert, ECF volume depletion is mild with slight or no change in blood pressure and renal function, the fluid of choice is oral free water. If a patient has a serum Na^+ higher than 160 mmol/L and shows confusion, disorientation, tremulousness, nystagmus and Babinski's sign, and impaired renal function, **fluid of choice is 5 percent dextrose in water**. It should be administered at a rapid rate to repair 50 percent of the deficit in 12 hours. The remaining deficit may be corrected rather slowly over a period of 48 to 72 hours. Blood glucose level should be monitored and regular insulin will be used to control hyperglycemia and prevent further free water loss. The amount of fluid to be administered may be calculated by using the following formula.

In a given patient for example, serum Na is 160 mEq/L and to bring serum Na down to 140 mEq/L, how much free water is to be given:

$$= \frac{160 - 140}{160} \times 100 = 12.5 \text{ percent water deficit}$$

Estimate the current weight or obtain the actual weight of the patient. For example, the weight in question is 70 kg. Sixty percent of 70 kg is 42 liters of water. 12.5 percent of 42 liters is 5.25 liters which is the water deficit. Similarly, in a given patient who is unresponsive and serum Na is 180 mmol/L and his current weight is 70 kg, the water deficit will be 22.2 percent.

$$= \frac{180 - 140}{180} \times 100 = 12.2 \text{ percent water deficit}$$

Again total body water in a 70 kg individual is 42 liters. Thus 22.2 percent deficit of 42 liters is 9.32 liters.

Oral Correction

Free water ingested orally is the safest and simplest treatment. It is appropriate, however, only in patients who are alert and oriented and who have no change in blood pressure or renal function. Patients should drink 300 ml of water every 2 hours for 16 hours while they are awake and 300 ml upon waking during the sleep period.
The total daily intake should be approximately 2400
2700 ml of water, taking into account any insensible wa
loss; febrile persons should drink an extra one to t
liters. The regimen should continue until serum sodiu
is equal to or less than 145 mEq/L.

Intravenous Therapy

In a confused or unresponsive patient, intraveno
treatment will be necessary. The ideal IV solution
treating hypernatremia is 5 percent dextrose in wat
which provides free water as the dextrose is oxidized. T
infusion also increases the glomerular filtration rate a
enhances excretion of sodium and nitrogenous wast

It is important to make sure that correction is
dangerously rapid. Although the speed of infusi
probably does not affect survival, a too rapid decre
in ECF space osmolality may cause abrupt fluid shi
resulting in cerebral edema and grand mal seizu
Lateral pontine and extrapontine myelinosis can a
be associated with rapid correction or overcorrect
of hypernatremia and hyperosmolality. The fluid
should be adjusted so that plasma sodium is redu
by no more than 0.5 mmol/L each hour or 12 mm
in the first 24 hours. Thereafter, infusion rate is redu
to avoid decrease of serum Na by no more than 5
mmol/L per 24 hours. Intravenous therapy is contin
in an unresponsive patient until serum Na is redu
to 145 mmol/L or less. Therapy should be switc
to oral administration once the patient beco
alert and serum sodium level has been decrease
near normal or normal level. Electrolytes shoul
monitored frequently to ensure that serum sodium
not decrease too rapidly. To control hyperglycem
diabetic patients, small doses of regular insulin,
as 20 units, may be added to infusion bag or g
subcutaneously on a standard sliding scale. Contr
hyperglycemia will minimize further free water los

Adjuvant Therapy

1. Check serum potassium and magnesium 12 h
and replace them accordingly.
2. Aqueous vasopressin (Pitressin®) 5 units subcutane
every 6 to 8h can be prescribed to promote free
absorption x 48h.
3. Alternatively, dDAVP (desmopressin), a synthetic a
of vasopressin 0.5 to 1 mcg subcutaneously ever
will promote free water absorption and is effectiv

A patient is presented here to exemplify the comprehensive management plan of hypernatremia.

Patient #5

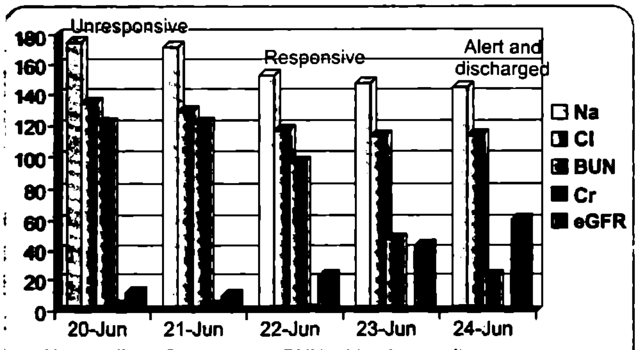
ES 88-year-old white female was brought into emergency room of a local hospital from a nursing home on June 20, 2010. She was unresponsive and dehydrated. Her admission laboratory is shown in Table 4. She was severely hypernatremic and renally impaired. Five percent dextrose was started at a rate of 300 ml/h in the emergency room. She was then treated with graded doses of 5 percent dextrose in water infusion and free water 200 ml every 4 hours through nasogastric tube. She additionally received aqueous Pitressin® 5 units subcutaneously every 6 hours for 48 hours. Her hospital course is shown in Figure 3.

Her serial serum glucose levels and therapy to reduce serum glucose levels are shown in Table 5. Her admission serum uric acid was very high. This markedly elevated uric acid level could be the result of severe dehydration and both could have led to severe renal failure. Therapy and progressive decrease of serum uric acid is show in Table 6.

Note that giving normal or even half normal saline is deleterious to hypernatremic patients and will, in fact, further impair the cognitive function and increase the risk of death. Normal saline may increase blood pressure and urine output but impairment of cognitive function will outweigh these small benefits. Therefore any form of saline infusion should be avoided in hypernatremic patients. **The rationale for not using saline infusions will be presented later.**

Table 4. Admission lab for ES 88y white female

Na (mmol/L)	174
K (mmol/L)	4.6
Cl (mmol/L)	134
CO_2 (mmol/L)	33
Glucose (mg/dL)	295
BUN (mg/dL)	121
Cr (mg/dL)	3.85
eGFR (ml/min)	12
Calcium (mg/dL)	9.1
Cr = serum creatinine. 5 percent dextrose in water infusion was started at a rate of 300 ml/hour	



Na = sodium; Cl = chlorine; BUN = blood urea nitrogen; Cr = creatinine; eGFR = estimated glomerular filtration rate.

Figure 3: Hospital course for ES 88 y white female, June 20–24, 2010

Table 5. Serum glucose levels for ES 88y white female

1. Regular insulin 20 units per liter of 5 percent dextrose in water infusion bag
2. Accucheck Q4 hour
3. Regular insulin on a sliding scale given subcutaneously

June 2010	*mg/dL*
20	295
21	355
22 Insulin dose adjusted downward	32
22 Insulin dose adjusted	203
22 Fingerstick glucose	339
23 Fingerstick glucose	93
24 Fingerstick glucose	120
24 Fingerstick glucose	150

Table 6. Serum uric acid levels for ES 88y white female

June 2010	*mg/dL*
20	19.2
Allopurinol 600 mg administered through nasogastric tube daily x 3 days, 300 mg daily x 3 days, then 150 mg daily	
22 am	15.2
22 pm	12.2
23	10.5
24	6.8

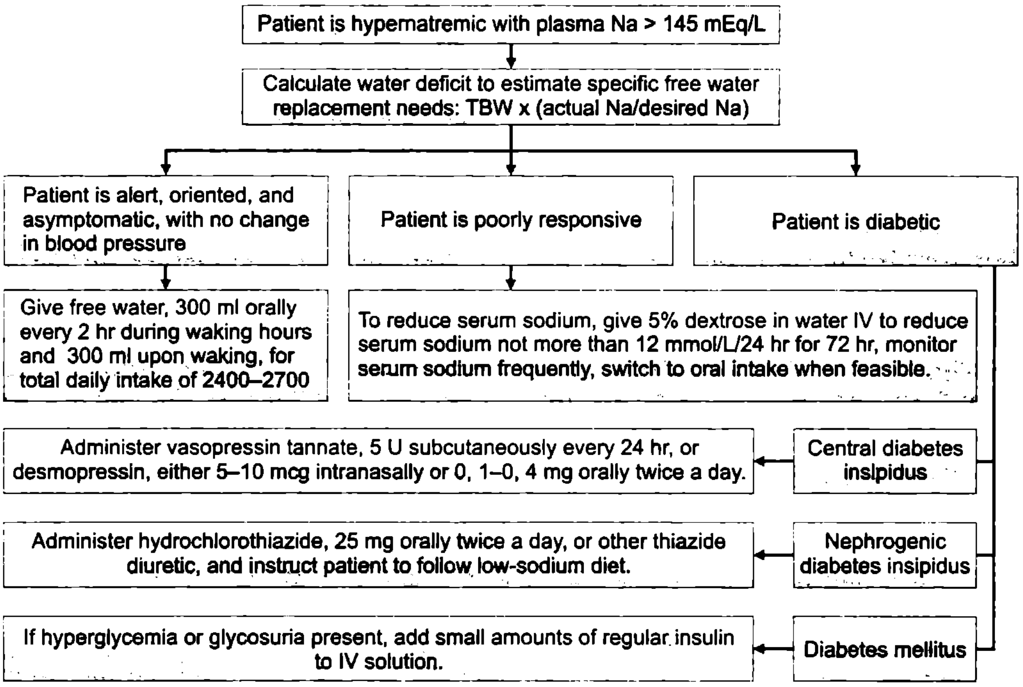

Patient is hypernatremic with plasma Na > 145 mEq/L
Calculate water deficit to estimate specific free water replacement needs: TBW x (actual Na/desired Na)
Patient is alert, oriented, and asymptomatic, with no change in blood pressure
Patient is poorly responsive
Patient is diabetic
Give free water, 300 ml orally every 2 hr during waking hours and 300 ml upon waking, for total daily intake of 2400–2700
To reduce serum sodium, give 5% dextrose in water IV to reduce serum sodium not more than 12 mmol/L/24 hr for 72 hr, monitor serum sodium frequently, switch to oral intake when feasible.
Administer vasopressin tannate, 5 U subcutaneously every 24 hr, or desmopressin, either 5–10 mcg intranasally or 0, 1–0, 4 mg orally twice a day.
Central diabetes insipidus
Administer hydrochlorothiazide, 25 mg orally twice a day, or other thiazide diuretic, and instruct patient to follow low-sodium diet.
Nephrogenic diabetes insipidus
If hyperglycemia or glycosuria present, add small amounts of regular insulin to IV solution.
Diabetes mellitus

Figure 4: An algorithm for treating hypernatremia.

Diabetes

Patient suffering from any form of diabetes require careful monitoring. Those with diabetes mellitus will of course require insulin. Those with central diabetes insipidus should receive antidiuretic agents. Recommended dose is 5 units of vasopressin tannate subcutaneously every 24 to 72 hours. Alternatively, twice-daily doses of 5 to 10 mcg of intranasal desmopressin or 0.1 to 0.4 mg of oral desmopressin may be used. Desmopressin 0.5 to 1 mcg can also be given subcutaneously twice daily. Serum electrolytes should be monitored to prevent development of acute hyponatremia and cerebral edema. The treatment plan of hypernatremia is presented in an algorithm. In patients with nephrogenic diabetes insipidus, hormone replacement is ineffective. Recommended therapy is a low-sodium diet and possibly a thiazide diuretic, such as hydrochlorothiazide, 25 mg per oral twice a day orally, to reduce solute delivery to diluting segments. Lithium-induced nephrogenic diabetes insipidus may be treated with amiloride 5 mg per oral twice daily. Amiloride blocks the sodium channel within the collecting ducts epithelium, thereby reducing lithium entry into cells and decreasing cellular toxicity.

The overall management of hypernatremia in algorithmic fashion is presented in Figure 4.

Lessons to be Learned

The following lessons may be learned from this communication:

1. From our previous study, as well as all the illustrations presented in this study, it is evident that rapid development of hypernatremia causes cognitive dysfunction or worsens cognitive impairment. Restoration of serum sodium level to normal with repletion of free water is paralleled by improvement of cognitive function. Therefore, cognitive impairment may be an important cause and effect of sustained hypernatremia among the hospitalized elderly subjects.
2. The most common type of fluid used in a hospital setting is normal saline. Hypernatremic patients have the reduced capacity to excrete sodium load. Even one half (0.5) of normal saline will not correct hypernatremia and will frequently exacerbate it. This is exemplified by the following mathematical manipulation:

Mathematical Manipulation of Increase of Serum Na with Normal Saline Infusion

- 70 y Serum Na 160 mmol/L weight 70 kg
- 2.5 liters of normal saline in 24 hrs
- Urine output 800 ml
- Insensible water loss 500 ml
- Total water loss = 1300 ml
- Urinary Na 15 mmol/L
- Gain of Na: Normal saline contains 154 mEq Na per liter
  2.5 liters x 154 = Na 385 mmol/L
- Loss of Na: 15 x 0.8 = 12 mEq
- Net Na gain = 385 - 12 = 373 mmol/L
- Net water gain = 2500 ml - 1300 = 1200 ml = 1.2 liters
- Estimated body water in this 70 kg person is 42 liters
- Expected increase of Serum Na = 373 / 42 + 1.2 = 8.6 mmol/L

3. Saline solution (normal, half normal, quarter normal) is unsafe in hypernatremic patients.
4. Plain (free) water orally or 5 percent dextrose in water is a safe fluid for hypernatremic patients.
5. Lateral pontine and extrapontine myelinolysis can be associated with rapid or overcorrection of hypernatremia and hyperosmolality. Also, rapid correction of hypernatremia may lead to grand mal seizures caused by rapid decrease of ECF osmolality and shift of water from ECF space to ICF space and resulting in cerebral edema.
6. Potassium chloride should be added in the dextrose solution bag from the beginning to prevent development of hypokalemia, which may precipitate pontine myelinolysis.

KEY POINTS

1. Hypernatremia is most common in the elderly, those living alone, or those living in a nursing home.
2. Frequently, they are disabled and hypodipsic.
3. Inability to drink fluid is the underlying mechanism.
4. Free water in the form of plain water orally and/or 5 percent dextrose in water infusion are the cornerstone of therapy.
5. Aqueous Pitressin® or dDAVP is an adjuvant therapy to promote free water absorption through renal tubules.
6. Mortality is high in those who are continuously infused with normal saline (hospital-acquired hypernatremia).

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5

Hypokalemia: Prevention and Treatment

Anil K Mand

INTRODUCTION

Hypokalemia is a common disorder in any discipline of practice of medicine. Most commonly, this electrolyte abnormality is brought into attention of the doctors or nurses by the clinical laboratory personnel. Even though patients with hypokalemia are often asymptomatic, but serious cardiac arrhythmias can develop and lead to cardiac arrest and death as a result of unrecognized and untreated severe hypokalemia. Current medical practice involves increasing number of elderly people, and many of these people are hypokalemic due to low intake of potassium. Since these elderly subjects often have ischemic heart disease or congestive heart failure (CHF) and are treated with one or more than one diuretic, incidence of severe hypokalemia is likely to climb. Hence, importance of disorder of hypokalemia is quite high, thus prompt recognition and treatment of this disorder is essential to avert catastrophe. This article is aimed to succinctly present the pathophysiology of hypokalemia and lucidly describe the prevention and treatment strategies.

PATHOPHYSIOLOGY

Potassium is the major intracellular cation. The total potassium content of the body averages 3,500 mmol (55 mmol per kg body weight); 98 percent of which is in the intracellular fluid. Only 2 percent potassium is in the extracellular fluid. Although extracellular potassium is a fraction of the total body potassium, it exerts profound effects on the function of the organ systems. The extracellular or serum potassium is maintaine within normal limits by the flux of potassium betwee the extracellular and intracellular fluid spaces; howeve when this concerted balance is offset, changes in serur potassium become overt. Normal persons who consum a typical Western diet ingest approximately 70 mmc of potassium per day. The small intestines, especiall jejunum, absorb virtually all of the ingested potassiur and deliver it to the liver for processing by means of th hepatoportal circulation.

In a balanced state of potassium, 80 to 85 percer of daily intake of potassium is excreted by the kidney The remaining amount of potassium intake is most excreted by the gastrointestinal tract. A small fraction potassium is excreted in the sweat. Potassium is filtere by the glomeruli and almost completely reabsorbe by the proximal tubule and ascending limbs of loop Henle. Potassium is secreted by the principal cells the collecting tubules, and most of this potassium excreted in the urine. Principal cells, which compri 70 to 75 percent of the collecting tubule cells, media sodium reabsorption and potassium secretion ar are targets for angiotensin II, aldosterone, aldostero receptor antagonists, and potassium-sparing diureti Factors that regulate principal cell potassium secreti include potassium intake, intracellular potassium lev sodium delivery to the collecting tubules, urine fl rate, and hormones, such as aldosterone and bet catecholamines.

The kidneys are the major organs for exterr potassium balance or homeostasis; therefore, excessi loss of potassium through the kidneys eventually leads of hypokalemia. In response to a high-potassium meal, that includes glucose, pancreatic insulin secretion activates skeletal muscle and liver Na, K-ATPase, which pumps potassium from the plasma to intracellular fluid of these cells. This mechanism minimizes the postprandial increase in plasma potassium concentration.

To maintain balance, the amount of potassium consumed in the meal (minus the small amount lost in the feces) is secreted into the urine. When potassium consumption increases plasma potassium concentration, it triggers aldosterone synthesis and release from the adrenals, which stimulates the activity and synthesis of NA, K-ATPase, and luminal potassium channels in collecting tubule principal cells to secrete excess potassium and restore the balance. Aldosterone also enhances potassium secretion in the distal colon. This pathway of potassium loss can be a very important source of protection against hyperkalemia when renal function is severely decreased. Conversely, if potassium intake is low or its output is very high, plasma potassium concentration decreases and feedback regulation redistributes potassium from intracellular fluid to plasma and minimizes renal potassium excretion.

Acid-Base Status

It is well known that extracellular acidosis or academia produces hyperkalemia due to efflux of potassium from inside the cells consequent to intracellular acidosis; whereas extracellular alkalosis or alkalemia produces hypokalemia due to influx of potassium inside the cells. This is not an invariable phenomenon as exemplified by hypokalemia in proximal (Type II) and distal (Type I) renal tubular acidosis (RTA), but hyperkalemia in Type IV distal RTA. However, in metabolic acidosis, unless there is a potassium leak, as in proximal or distal RTA, potassium load is not well tolerated. In metabolic alkalosis, although hypokalemia has been claimed to be due to alterations in internal potassium balance, urinary loss of potassium could account for a large part of hypokalemia. The situation is different in respiratory acid-base disorders. Both acute and chronic respiratory alkalosis has slight effect on internal or external potassium balance with a mild tendency to hypokalemia. Conversely, in chronic respiratory acidosis, high pCO_2 and enhanced bicarbonate reabsorption is accompanied by excessive urinary potassium loss and hypokalemia.

Insulin

Insulin stimulates intracellular uptake of potassium and can rapidly reduce extracellular potassium concentration. This is likely to occur after a high carbohydrate meal in individuals with normal pancreas. Conversely, in diabetes mellitus the deficiency of insulin will increase the propensity to hyperkalemia. However, this proneness to hyperkalemia is mitigated by the osmotic diuresis and accompanying kaliuresis in uncontrolled diabetes mellitus. Therefore, patients with diabetes mellitus generally do not develop hyperkalemia unless they develop diabetic ketoacidosis, hyporeninemic hypoaldosteronism or renal failure. In fact, untreated or uncontrolled diabetic who have marked polyuria are often hypokalemic.

Catecholamines

Among the catecholamines, epinephrine influences internal potassium influx and produces hypokalemia without increasing urinary excretion of potassium, suggesting shift of potassium from the extracellular fluid to intracellular fluid. Hypokalemic effect of epinephrine can be demonstrated by infusion of epinephrine into man or animal. The importance of intracellular translocation of potassium induced by epinephrine in normal conditions is unclear; however, this effect offers a potentially protective mechanism against life-threatening hyperkalemia in patients with massive trauma, postsurgery, or rhabdomyolysis. Each of these conditions may result in a massive release of intracellular potassium. With decreased function of the kidneys, ability to excrete potassium load is diminished, but internal shift of potassium provides a protection against dangerous hyperkalemia in states of potassium overload. In this context, it is worth emphasizing that use of beta-blockers that blunt epinephrine effect is not safe in hypertensive patients with renal failure.

After consideration of the factors that control external and internal potassium homeostasis, the causes of hypokalemia can be appropriately defined. It is important to reiterate that among all these factors, high renal excretion of potassium determines most cases of hypokalemia.

CAUSES OF HYPOKALEMIA

Normal serum potassium level ranges from 3.5 to 5.0 mmol/L. Serum potassium level less than 3.5 mmol/L is called hypokalemia. Severity of hypokalemia is determined on the basis of serum potassium levels. There is no easy method to determine body potassium content. Thus, severity of hypokalemia is defined as:

- Mild when serum K is 3 to 3.5 mmol/L
- Moderate when serum K is 2.5 to 3 mmol/L
- Severe when serum K is <2.5 mmol/L.

The Common Causes of Hypokalemia

Diuretic Therapy

Diuretic therapy is the most common cause of hypokalemia of all severity. All diuretics—whether thiazides, loop diuretics, or carbonic anhydrase inhibitors—produce hypokalemia of variable severity. Diuretics do not produce hypokalemia immediately after initiation of therapy, unless the patient has an underlying condition that enhances potassium excretion. Thus, prompt appearance of hypokalemia following diuretic therapy is an indication of a pre-existing covert renal potassium leak condition, such as primary or secondary hyperaldosteronism. It is generally understood that severe hypokalemia is less common in hypertensive patients treated with a diuretic, whereas severe hypokalemia is more common in patients with nephrotic syndrome, cirrhosis of liver, or CHF treated with an equivalent dose of a diuretic and consuming almost equal amounts of potassium in the food.

Alcoholism

Alcoholics brought to the emergency room reveal a panorama of metabolic problems, consisting of hypokalemia, hypophosphatemia, and hypomagnesemia. Hypokalemia is the most common abnormality found and is due to multiple factors, including poor intake of potassium, gastric loss of potassium through vomiting, and urinary loss of potassium.

Severe Vomiting and Gastrointestinal Suction and Drainage

Patients with severe vomiting or gastrointestinal suction and drainage following surgery frequently develop severe hypokalemia. Hypokalemia is partly due to gastric loss of potassium and partly due to renal loss of potassium. A sequence of events begins with volume depletion and leading to hyperreninemia and hyperaldosteronism that accounts for the renal loss of potassium.

Severe Diarrhea

Severe diarrhea is becoming a common cause of severe hypokalemia in the hospital setting. The most common cause of severe diarrhea is *Clostridium difficile* infection. The extent of K loss in the diarrheal stool is difficult to determine as no method is readily available. However, repeated urinary K analysis reveals that hypokalemia in diarrheal state is not due to urinary loss of potassium.

Primary or Secondary Hyperaldosteronism

Hypokalemia in a hypertensive patient in the absence of diuretic use should alert a physician about the possibility of primary aldosteronism (aldosterone producing tumor, bilateral adrenal hyperplasia) or secondary hyperaldosteronism due to renal artery stenosis or renin-secreting tumor.

Renal Tubular Acidosis

Distal (Type I) and proximal (Type II) RTA are commonly associated with kaliuresis and hypokalemia. In proximal RTA, kaliuresis is due to increase in the delivery of bicarbonate to the distal secretory sites, resulting in increase in potassium secretion. In distal RTA, where hydrogen ion secretion is defective, excessive potassium secretion occurs in order to facilitate sodium reabsorption. Hypokalemia is more severe in dista RTA than in proximal RTA and frequently a presentin feature due to severe myopathy caused by hypokalemia Recurrent abdominal or flank pain accompanied by gros hematuria and passage of stone, as shown in Figure 1, i

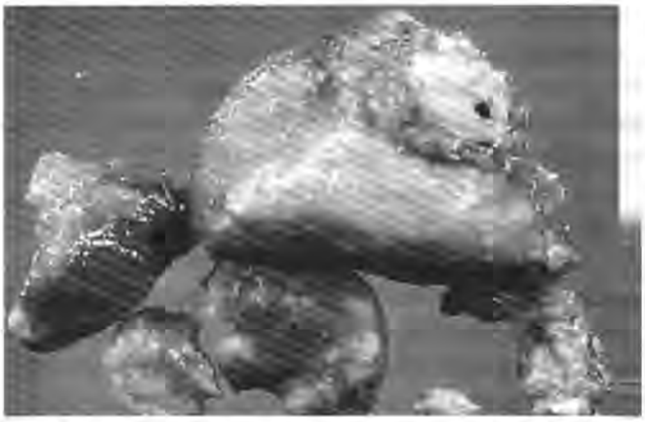


Figure 1: 35-year-old white female with classic distal R characterized by severe hypokalemia, persistent metabo acidosis, and bilateral nephrolithiasis with recurrent passa of stones (*For color version, refer to plate 1*)

also a common presenting feature of distal RTA. Severe hypokalemia in distal RTA is in part due to associated high aldosterone level as correction of hypokalemia is facilitated with the use of aldosterone antagonist, spironolactone, in addition to potassium intake.

The Uncommon Causes of Hypokalemia

Leukemia

Moderate to severe hypokalemia is very common in acute myelocytic or myelomonocytic leukemia. Hypokalemia has been attributed to lysozymuria in these types of leukemia. The exact mechanism(s) by which lysozyme excretion induces kaliuresis and hypokalemia are unknown.

Hypokalemia Associated with Ectopic Adrenocorticotrophic Hormone Production

Tumors, especially small cell-type bronchogenic carcinoma, may produce an adrenocorticotrophic hormone that stimulates cortisol and aldosterone production and, thereby, enhances urinary potassium loss. Hypokalemia can be intractable and would require large amounts of potassium supplement to control hypokalemia.

Hypokalemia Induced by Antibiotic

Many antibiotics, including penicillin, carbenicillin, and gentamicin, produce hypokalemia. Hypokalemia is due to excessive secretion of potassium, which occurs in order to dissipate luminal electronegativity caused by penicillin or carbenicillin. However, the mechanism is different for hypokalemia in gentamicin therapy. Renal cortical tissue after gentamicin administration demonstrates excessive numbers of lysosome. These lysosomes have been found to be the storage source of lysozyme, resulting in lysozymuria and consequent hypokalemia. Amphotericin B produces hypokalemia secondarily to distal (Type I) RTA.

Magnesium Depletion

Hypomagnesemia is a concomitant abnormality with hypokalemia and is seen commonly in patients treated with a loop diuretic, with malabsorption syndrome, and in alcoholics. Magnesium is reabsorbed in the ascending thick limb of Henle's loop and, hence, reabsorption is inhibited by loop diuretics. Consequently, magnesium wasting is common in users of a loop diuretic. Magnesium wasting also occurs during gentamicin and cisplatin therapy. The mechanism(s) by which hypomagnesemia causes hypokalemia is unknown; however, it should be stressed that hypomagnesemia could delay correction of hypokalemia with only potassium supplementation. This will be discussed in detail in the section on the management of hypokalemia.

Bartter's Syndrome

Bartter's syndrome is chiefly found in children and young adults. Short stature, failure to thrive, muscle weakness or cramps, polyuria and nocturia are the usual presenting features. The characteristic features include hypokalemia, hyperreninemia, and hyperaldosteronism. The latter are thought to be due to hyperplasia of the juxtaglomerular apparatus. Blood pressure is normal or high. High urinary PGE2 associated with hyperplasia of the renal papillary interstitial cells have been observed. Hypokalemia, induced in experimental animals, has shown hyperplasia of the collecting tubule cells and renal papillary interstitial cells, both of which are a source of PGE2. Therefore, it appears that hypokalemia is a primary event, and excessive PGE2 production is a secondary event. Further studies have shown that excessive urinary chloride >100 mmol/L is a characteristic feature of Bartter's syndrome. One of the sites of action of PGE2 is the ascending thick limb of Henle's loop. Possibly PGE2 inhibits chloride reabsorption and accounts for the excessive loss of chloride in the urine. The delivery of large amounts of sodium and chloride in the distal and collecting tubules could, in part, be responsible for the excessive potassium secretion and kaliuresis. Surreptitious diuretic use and magnesium depletion produce manifestations similar to Bartter's syndrome and are called pseudo Bartter's syndrome. Defect in sodium and chloride reabsorption results also in loss of a cotransporter, calcium. Thus, hypercalciuria is common in Bartter's syndrome.

Gitelman's Syndrome

Gitelman's syndrome is a variant of Bartter's syndrome but is seen commonly in older persons. Unlike Bartter's syndrome, Gitelman's syndrome is associated with hypocalciuria. Further, hypomagnesemia is common in Gitelman's syndrome.

Liddle's Syndrome

Liddle's syndrome is the reverse of Bartter's syndrome, except hypokalemia. This syndrome comprises low plasma renin activity, low plasma aldosterone level, and elevation of blood pressure. This syndrome apparently is the result of an unknown circulating mineralocorticoid and, consequently, hypervolemia from Na^+ and water retention. Hypervolemia will increase blood pressure and decrease plasma renin activity. Recently, a genetic defect in sodium channel has been identified. This defect results in excessive reabsorption of sodium and loss of potassium.

Hypokalemic Familial Periodic Paralysis

As the name implies, it is familial. The condition is characterized by intermittent sudden episodes of severe muscle weakness to paralysis of the lower extremities or of all four extremities. This episodic paralysis is almost invariably accompanied by severe hypokalemia. Hypokalemia is due to an abnormality in the internal potassium homeostasis leading to rapid shift of potassium from the extracellular fluid into the intracellular fluid. These episodes are precipitated by a high carbohydrate meal, glucose, insulin, epinephrine, or even severe anxiety with accompanying respiratory alkalosis, and possible outpouring of epinephrine.

Chronic Laxative Use

Laxative (licorice) contains glycyrrhizic acid, which tends to promote sodium reabsorption leading to hypervolemia and hypertension as a result of mineralocorticoid excess. In the state of mineralocorticoid excess, the enzyme that converts cortisol to cortisone is inactivated allowing higher levels of cortisol. Plasma renin activity and plasma aldosterone level are low, thus mimicking Liddle's syndrome.

In summary, causes of hypokalemia can be divided into two groups: A. common causes; B. uncommon causes.

A. Common Causes of Hypokalemia
   1. Diuretic therapy
   2. Persistent vomiting
   3. Postsurgery gastrointestinal suction
   4. Severe relentless diarrhea
   5. Alcoholism
   6. RTA
   7. High aldosterone/ACTH states
   8. Low intake - often unrecognized.

B. Less Common Causes of Hypokalemia
   1. Bartter's Syndrome/Gitelman's Syndrom Liddle's Syndrome
   2. Familial periodic paralysis
   3. Thyrotoxic periodic paralysis
   4. Laxative or diuretic abuse
   5. Drugs—penicillin, amphotericin B, gentamici cisplatinum
   6. Leukemia

Low Intake of Potassium

As current medical practice involves increasing numb of elderly and disabled population in the hospit setting, incidence of hypokalemia is high among tl hospitalized patients. Frequently, no cause is identifi to account for hypokalemia. Most likely hypokalemia these population is due to poor intake of foods that a rich in potassium, such as meat, fruits, fruit juice, ar green vegetables. Poor intake of potassium coupled wi obligatory renal loss of potassium, which is 10 to 15 mm per day, makes hypokalemia worse.

CLINICAL MANIFESTATIONS OF HYPOKALEMIA

The vast majority of the patients with hypokalemia a asymptomatic. Potassium, being the major intracellul cation, muscles cells are most severely affecte in potassium depletion syndrome. Therefore, tl manifestations of hypokalemia are largely ascribed to tl functional derangements of skeletal and heart muscl and smooth muscles of the gastrointestinal tract.

Manifestations of Skeletal Muscle Dysfunctio

The major skeletal muscle dysfunction is myopath Myopathy gives rise to weakness or paralysis of tl extremities. Worsening of the weakness with exerci tends to support the diagnosis of hypokalemic myopath The lower extremities are affected more than the upp extremities. Patients with familial periodic paralys present with marked weakness of both lower extremi or sometime all four extremities. In untreated seve hypokalemia (serum potassium <2.5 mmol/L), myopatl may progress into rhabdomyolysis and myoglobinuri acute renal failure may eventuate. These myopath complications are more common in hypokalemia dı to alcoholism than in hypokalemia due to other cause in rare patients, accessory muscles of respiration and diaphragm may be paralyzed leading to acute respiratory distress or even acute respiratory failure.

Cardiac Manifestations

Incidence of cardiac manifestations increases in those with CHF, in those treated with digitalis and/or with a history of myocardial infarction. The electrocardiographic findings are nonspecific and consist of ST and T wave changes. Prominent U wave is considered characteristic of hypokalemia. Infrequently, and especially in patients treated with digitalis, ventricular premature contractions, supraventricular tachycardia, or atrial fibrillation with rapid ventricular response may supervene. Hypokalemia of any severity can predispose to ventricular tachycardia, ventricular fibrillation, and cardiac arrest in patient with CHF. Here is an example:

In Mississippi-belt area, an 84-year-old white female with history of CHF was admitted into a local hospital. She was treated with digitalis, diuretics, and potassium supplement. At the time of discharge, her serum potassium was 3.4 mmol/L. Potassium supplement was not prescribed to continue at home. Shortly after discharge to home, patient developed cardiac arrest and died. Patient's family filed a lawsuit stating that cardiac arrest was due to low serum potassium as no potassium supplement prescribed. The author of this article was consulted by the attorneys of the family from the Mississippi belt with regard to cardiac disorders associated with hypokalemia.

Long QT Syndrome and Torsade de pointes

This syndrome may be inherited or acquired, caused by malfunctions of the ion channels responsible for ventricular depolarization. Potassium and/or magnesium depletion are the main metabolic disorders associated with ion channel malfunction and hence predispose to arrhythmias. The characteristic presenting feature in torsade de pointes is syncope or cardiac arrest.

Hypokalemia can compound the effects of class III antiarrhythmic agents, such as sotalol, and predisposes to arrhythmias. Torsade de pointes has been reported in 2 to 4 percent of patients treated with sotalol, a beta blocking drug. This risk is increased in older patients and in those with renal impairment. Treatment is correction of hypokalemia and hypomagnesemia (See Table 1).

Renal Manifestations

Morphologically, proximal renal tubule cells and, to an extent, distal renal tubule cells show excessive vacuole formation. The papillary interstitial cells show excessive granularity in hypokalemic rat kidneys.

Table 1. 74 y white male with a history of congestive heart failure. Premature ventricular contractions have developed. He also has a history of renal insufficiency

Lab:	August 03, 2007
	Na$^+$ 142 mmol/L, K$^+$ 3.1 mmol/L, BUN/Cr 30/2.32 mg/dL, eGFR 29 ml/min
Office visit:	August 30, 2007
	Irregular heart R/O, atrial fibrillation, edema ++, BP 140/60
Medication:	Amlodipine 10 mg po bid, doxazosin 4 mg once daily, metoprolol 50 mg po bid, furosemide 40 mg once daily po, metolazone 5 mg po once daily
Plan:	ECG, ↑ metolazone 10 mg po daily, start KCl 20 mEq po bid, amiloride 1.25 mg po bid
ECG:	August 30, 2007
	Premature ventricular and atrial complexes
Lab:	September 04, 2007
	Na$^+$ 138 mmol/L, K$^+$ 4.3 mmol/L, BUN/Cr 37/1.96 mg/dL eGFR 36 ml/min, magnesium 1.4 mg/dL
Prescription	Magnesium 400 mg po 3 times daily
ECG	September 17, 2007
Lab:	Na$^+$ 139, K$^+$ 4.7, BUN/Cr 29/1.57, eGFR 46 ml/min
None	Premature ventricular complexes
Rare	Premature atrial complexes
ECG	Almost normal

Cr = serum creatinine; eGFR = estimated glomerular filtration.

Clinically, there may be no symptoms or there may be history of polyuria and polydipsia. Polyuria is the result of ineffective vasopressin at the collecting tubules. As mentioned earlier, hypokalemia seems to enhance production of prostaglandin E2, which inhibits adenyl cyclase. Consequently, there is no or slight formation of cyclic AMP, which is essential for the action of vasopressin. Due to ineffective vasopressin, a polyuric syndrome resembling diabetes insipidus (nephrogenic diabetes insipidus) may supervene. Renal insufficiency is not uncommon, but progressive renal failure is rare. Intracellular fluid, devoid of potassium, retains sodium and water causing an increase in total body water. Thus, body weight increases. This phenomenon has a remarkable therapeutic implication and will be discussed in detail in the section on management.

Endocrine Manifestations

In hypokalemic state, release of insulin from the pancreas is blunted, resulting in hyperglycemia. Hyperglycemia is a very common finding in patients treated with a diuretic. Hyperglycemia does not always abate with restoration of the serum potassium to normal level. This raises the possibility that diuretic itself in some way may precipitate hyperglycemia or uncover diabetes mellitus.

Manifestations of Gastrointestinal Smooth Muscle Dysfunction

Severe hypokalemia (serum potassium ≤2.5 mmol/L) is often associated with severe hypomagnesemia (serum magnesium ≤1 mg/dL) and can give rise to gastrointestinal dilatation to the point of paralytic ileus or megacolon. Clinically, patient may present with vomiting, constipation or diarrhea, and abdominal distension. A patient is presented here to illustrate that problem.

Table 2. Serum chemistry, January 11, 2001

Serum Chemistry	*Jan 11, 2001*
Glucose (mg/dL)	133
BUN (mg/dL)	14
Creatinine (mg/dL)	0.7
Sodium (mmol/L)	129
Potassium (mmol/L)	2.7
Chloride (mmol/L)	87
Carbon dioxide (mmol/L)	29

A 79-year-old white female was admitted to local hospital on January 11, 2001, with a diagnosi of megacolon (See Table 2.). She gave history o intermittent diarrhea and vomiting. She was noted t be hypokalemic of unknown etiology in the past an prescribed spironolactone. For some reason, she was no taking spironolactone prior to this admission. Her bloo pressure had been low normal to normal. Significan physical finding was markedly distended abdomen wit hyperactive bowel sounds (Fig. 2). A barium enem showed atonic megacolon (Fig. 3).

She was treated with normal saline infusio with added potassium chloride 40 mmol/L bag an

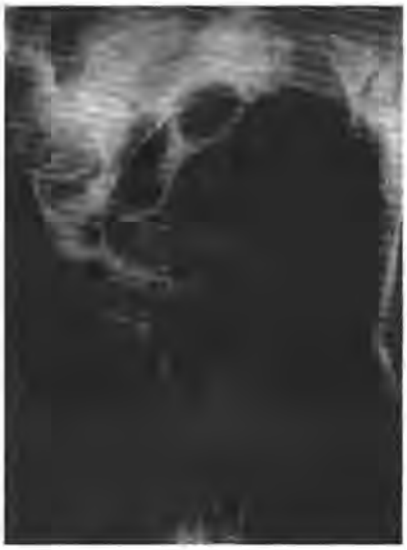


Figure 2: Distended abdomen

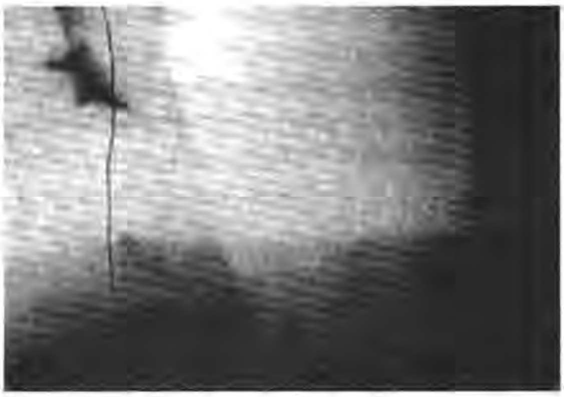


Figure 3: Atonic megacolon

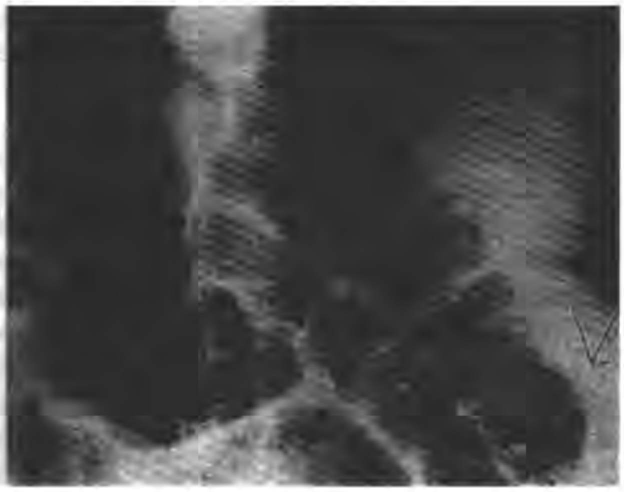


Figure 4: Decompression of megacolon

spironolactone 50 mg orally every 6 hours (total = 200 mg/24 hours). Her symptoms improved with increase in serum potassium and concomitantly decompression of megacolon (Fig. 4).

She did well. She continues to take spironolactone. Her serum chemistry of March 14, 2001, showed increase of serum potassium to normal and normal appearance of the colon by flat film of the abdomen (See Table 3).

DIAGNOSIS OF THE ETIOLOGY OF HYPOKALEMIA

1. In all cases of hypokalemia, complete history is mandatory. History of diuretic or laxative abuse, diarrhea, vomiting, or alcoholism is important.
2. In the laboratory study, the concomitant presence of hyperchloremia with nonanion gap ($Na^+ K^+ - Cl^- + HCO_3^-$) metabolic acidosis suggests RTA. Morning urine pH should be checked and, if the urine pH is consistently six or higher, diagnosis of distal (Type I) RTA becomes tenable. Further investigations include ultrasound of the kidneys for nephrocalcinosis or nephrolithiasis, 24-hour urinary study for hypercalciuria and low citrate excretion, and finally, in some cases, ammonium chloride test to confirm the diagnosis of distal RTA.
3. In the hypertensive patient, plasma renin and plasma aldosterone level should be obtained to distinguish between primary and secondary hyperaldosteronism. In primary hyperaldosteronism, plasma renin is low to very low as a result of excess volume, while plasma aldosterone level is elevated independent of renin activity with aldosterone/renin ratio >50. In secondary hyperaldosteronism, such as renal artery stenosis, both plasma renin and plasma aldosterone levels are elevated and the ratio of aldosterone/renin is low (<20).
4. An arterial blood gas analysis to differentiate metabolic acidosis from respiratory alkalosis with low CO_2 in renal panel.
5. Random urine sample analysis for sodium, potassium, chloride, and creatinine.

Table 3. Serum chemistry, January to March 2001

Serum Chemistry	Jan 11, 2001	Mar 14, 2001
Glucose (mg/dL)	133	73
BUN (mg/dL)	14	7
Creatinine (mg/dL)	0.7	0.4
Sodium (mmol/L)	129	136
Potassium (mmol/L)	2.7	4.2
Chloride (mmol/L)	87	98
Carbon dioxide (mmol/L)	29	29

Here are analyses from serum chemistry, blood gas analysis, and urinary analysis, which help in the diagnosis of the cause of hypokalemia:

- Metabolic Acidosis: Low pH, low HCO_3, low PCO_2.
- Metabolic Alkalosis: High pH, high HCO_3, high PCO_2.

Based on combination of findings:

1. Hypokalemic hyperchloremic normal anion gap metabolic acidosis - RTA Type I or Type II: urinary potassium is high.
2. Hypokalemic normochloremic metabolic alkalosis in a hypertensive patient: primary or secondary hyperaldosteronism: urinary potassium high.
3. Hypokalemic hypochloremic metabolic alkalosis. Serum sodium may or may not be low. High urinary chloride much higher than sodium. Bartter's syndrome or Gitelman's syndrome.
4. Hypokalemic hypochloremic metabolic alkalosis with very low urine chloride lower than sodium: vomiting, nasogastric suction.
5. Hypokalemic hypochloremic metabolic alkalosis with high urinary sodium and chloride and elevated BUN and serum creatinine; high urinary potassium: diuretic therapy.
6. Hypokalemic hyperchloremic metabolic acidosis (high anion gap) with elevated BUN and serum

creatinine; high urinary potassium: acute or chronic renal failure.

7. Hypokalemic metabolic alkalosis with normal urinary potassium: familial or thyrotoxic periodic paralysis.

TREATMENT OF HYPOKALEMIA

Essential Components

1. Low salt diet: reduced distal delivery of Na^+ reduces K^+ exchange with less urinary K^+ loss
2. Potassium Supplementation
3. Potassium Retaining Agents
4. Aldosterone Antagonists
5. Beta Blocker Therapy
6. Magnesium Supplementation
7. Adjuvant Therapy

Potassium Supplementation

K, 3.5 - 4 mmol/L

Questions: Should I replace potassium?

Answers: 1. No, if not on diuretic therapy; investigate and ensure adequate K intake in foods.

Yes, if patient has CHF, on digoxin therapy; history of myocardial infarction.

Yes, if patient is receiving a diuretic and it needs to be continued as in CHF. Dosage will vary depending on renal function. (See Table 4)

Potassium supplementation is essential when serum potassium is equal to or less than 3.4 mmol/L. Doses vary according to renal function.

Potassium Preparations and Administration

1. Potassium chloride (KCl) is the preparation of choice. KCl dissociates readily into K^+ and Cl^- ions, allowing reabsorption of K^+ and Cl^- ions at the expense of Na^+ and HCO_3^- reabsorption. HCO_3 is lost in the urine; thus, metabolic alkalosis is abated.
2. Oral replacement is adequate in most patients.
3. The average dose of KCl is 20 to 40 mEq orally 2 to 4 times daily depending on the severity of hypokalemia and renal function status. Reduce total dose if renal function is low. A patient with serum potassium o 2 mmol/L may have a total body potassium deficit of 800 to 1,000 mEq. Therefore, the recommended dosage is 40 mEq KCl orally 4 times daily, provided renal function is normal. Potassium chloride i available in liquid (elixir) or tablet form. The liqui or the elixir preparation is acrid. The acrid taste o the liquid preparation may be minimized by takin liquid KCl mixed in chilled water or orange juice. Th potassium chloride slow release tablet is available a Klor-con• (Ciba), which contains 8, 10, or 20 mEq o K^+ and Cl^-. The enteric coated or slow release table may produce intestinal ulceration and stenosi and is less safe than liquid preparation. Oral K therapy should be monitored by daily or twice dail measurement of serum K^+ and spot urinary sampl for K^+. Generally, serum K^+ begins to rise in 48 to 7 hours. The difference between total K^+ intake, whic includes supplements and food K^+; and urinary K loss, would suggest cellular K^+ utilization. If seru K^+ level does not appreciably rise by 72 hours, th possibility of concomitant magnesium depletio should be considered. During potassium replaceme therapy, depleted cells must be replenished before significant rise in serum K^+ can be seen. The cells ha $Na^+ - K^+$ pump, which intrudes K^+ and extrudes sodiu (Na^+). This pump is activated by the enzyme Na^+ – ATPase. The co-factor for this enzyme is magnesiu In severe magnesium deficiency state, activati of Na^+ -K^+ pump does not occur and, therefo the cells are not enriched with K^+. The evidence f this would be excessive loss of K^+ in the urine wi K supplementation. Therefore, it is imperative measure the serum magnesium level, if serum level does not rise in a reasonable period. If the seru magnesium is lower than normal (N=1.7 to 2.8 mg/d magnesium sulfate 50 percent 2 ml (1 gm) should administered by deep IM every 8 hours on day 1, ev 12 hours on day 2, and once on day 3. Magnesi

Table 4. Types, dosages and routes of administration of potassium supplements

Formulation	*Dose and Rate*	*Indication*
Oral potassium chloride (multiple formulations)	60 – 80 mEq/d in divided doses	Non urgent correction and/or maintenance
Intravenous potassium chloride	10–20 mEq/h in saline infusion Monitored serum K hourly	Cardiac arrhythmias, periodic paralysis or unable to tolerate oral dosing

Adapted from Kim GH, Han JS. Therapeutic Approach to Hypokalemia. Nephron 2002;92(Supp 1):28-32.

sulfate also is available as 10 percent solution. The equivalent dose will be 10 ml (1 g) instead of 2 ml with 50 percent solution; alternatively, magnesium sulfate may be administered orally 3 gm every 6 hours for 4 doses. Magnesium orally may produce severe diarrhea and interfere with potassium repletion.

4. Intravenous administration of potassium is not necessary except in cardiac arrhythmias with rapid ventricular response, familiar periodic paralysis and in severe myopathy with respiratory failure. In such situations, a patient must be admitted in the intensive care unit. Potassium chloride 100 mEq is mixed in a liter of normal saline, and the solution is infused at a rate of 100 ml/hour to deliver 10 mEq per hour. Administration must be continuously monitored. Rarely, in severe cardiac arrhythmias, in order to infuse more than 10 mEq KCl/hour, a mixture containing 200 mEq KCl in 500 ml normal or half-normal saline is prepared. This solution is infused at the rate of 50 to 100 ml per hour to deliver 20 to 40 mEq KCl per hour. As soon as cardiac rhythm returns to normal or respiratory muscle strength has been restored to normal, intravenous infusion is gradually tapered and discontinued, and KCl per oral is initiated. Serum K^+ levels should be monitored during the infusion and one hour after cessation of the infusion.

   Here is an example. (See also Tables 5 and 6.)

Number of Patients	40
Infusion	20 mmol of potassium chloride in 100 ml of normal saline over 1 hour
Administered Route	Central vein (n=26) Peripheral vein (n=14)
Method	Plasma potassium ([K]p) was measured at 15-minute intervals during and 1 hour after infusions in 31 patients.**

** Data limited to the 31 patients undergoing serial [K]p determinations.

Caution: No matter how low the serum K^+ level is and how alarming the cardiac arrhythmia, K^+ solution must never be injected directly. It must be mixed in a bag of normal or half normal saline. Human subjects have no ability to adapt rapidly to potassium load, which will lead to a life-threatening hyperkalemia, cardiac arrest, and instantaneous death.

5. Potassium-sparing drugs: These drugs include spironolactone, triamterene, and amiloride. All these drugs act in the cortical collecting tubule and inhibit secretion of potassium. Spironolactone acts by binding to aldosterone receptors and is effective in the presence of primary or secondary hyperaldosteronism; whereas triamterene and amiloride are effective independent of aldosterone. The mechanism(s) of action of triamterene and amiloride in retaining potassium are not clear; however, they inhibit a number of ATPase enzymes. The way by which inhibition of these enzymes causes retention of K^+ is quite intriguing.

Table 5. Plasma potassium concentration ([K]p) results (mmol/L)

	Mean ± SE	*Range*
Baseline [K]p	2.9 ± 0.08	2.0-3.7
Peak [K]p during infusion	3.5 ± 0.07	2.7-4.4
Postinfusion [K]p	3.4 ± 0.07	2.7-4.3
[K]p 1 hour postinfusion	3.2 ± 0.06	2.2-3.8

Data limited to the 31 patients undergoing serial [K]p determinations.

Table 6. Comparison of control vs. infusion electrocardiographic findings

	Control	*Infusion*
Heart rate (min^{-1})	97 ± 4	93 ± 5
PR interval (sec)	0.14 ± 0.005	0.14 ± 0.006
QRS interval (sec)	0.09 ± 0.005	0.09 ± 0.002
QT interval (sec)	0.32 ± 0.01	0.32 ± 0.01
T - wave amplitude in ECG lead II (mm)	0.19 ± 0.20	0.21 ± 0.21
Frequency of premature atrial beats (hr^{-1})**	11 ± 10	3 ± 2
Frequency of premature ventricular beats (hr^{-1})**	19 ± 7*	7 ± 2

* $P < 0.05$

** Data limited to the 31 patients with technically adequate cECG recordings.

Any one of these potassium sparing agents may be used as an adjuvant therapy with potassium chloride in situations such as congestive cardiac failure or nephrotic syndrome, where large doses of diuretic(s) sometimes have to be used and K^+ loss can be massive. In order to use the potassium sparing agent, one must ensure that renal function is normal or near normal. Potassium sparing agents retain potassium avidly, which, in the presence of renal insufficiency, could rapidly lead to hyperkalemia. Combination of K supplement and potassium sparing agent is recommended, as in congestive cardiac failure with diuretic infusion, nephrotic syndrome, cirrhosis of liver, Bartter's syndrome, or hypokalemia due to ectopic adrenocorticotrophic hormone syndrome where urinary K^+ loss is excessive.

Spironolactone (Aldactone•) (Searle) is available as 25 mg, 50 mg, or 100 mg tablets. The usual dose is 50 mg stat, then 25 to 50 mg every 6 hours. The effect does not start until after 48 hours. The total dose may reach up to 400 mg/day in primary hyperaldosteronism.

Common side effects include hyperkalemia, especially in the presence of renal insufficiency, and painful gynecomastia in men. The severity of gynecomastia, however, is related to dosage and duration of therapy. It is usually reversible following discontinuation of aldactone. Somewhat less common side effects include painful breasts, milk from breasts, and decrease in libido in females and impotence in males, and sodium depletion syndrome.

Triamterene (Dyrenium•) (SmithKline Beecham) is available as 50 or 100 mg capsules. Starting dose is 50 mg twice daily, but it may be increased up to 200 mg/day. Triamterene is available as combination product of 25 mg hydrochlorothiazide and 37.5 mg triamterene (Dyazide•) (SmithKline Beecham). This product is often used in the treatment of hypertension.

Common side effects include hyperkalemia, sodium depletion, especially with severe salt restriction, and metabolic acidosis. Uncommon side effects consist of megaloblastic anemia (especially in cirrhotics) and renal calculi. Acute interstitial nephritis has been reported.

Amiloride (Midamore•) (Merck, Sharp & Dohme) is available as 5 mg tablet. It is a very potent drug. The usual dosage is 5 mg daily; however, in severe hypokalemia 5 mg twice daily is recommended. A combination product called Moduretic• (Merck, Sharp & Dohme) contains 50 mg hydrochlorothiazide and 5 mg amiloride. The usual dose is one to two tablets daily in edematous conditio or in mild hypertension.

Side effects are minimal; however, hyperkalem may occur like that induced by other potassium spari agents.

In alcoholics, hypophosphatemia, hypocalcemi and hypomagnesemia occur concomitantly wi hypokalemia and replacement of each of these elemen becomes necessary.

Bartter's Syndrome/Gitelman's Syndrome

Bartter's Syndrome can be treated by a combination the following agents:

1. K^+ supplement
2. Spironolactone
3. Beta receptor blocker
4. Prostaglandin synthesis inhibitor
5. Angiotensin converting enzyme inhibitor

Potassium supplement and spironolactone may administered in the dosage as they were stated befo Beta blocker will inhibit renin production and can given orally as atenolol (Tenormin•) in a dosage of to 50 mg once daily. Prostaglandin synthesis inhibito including indomethacin or ibuprofen, appear to effective treatment in Bartter's syndrome. Vioxx 25 once daily per oral was found to be very effective correction of hypokalemia in Gitelman's syndrom This drug is no longer available in the United Stat but is available in other countries. Indomethacin given orally in a dosage 25 to 50 mg 3 to 4 times dail The side effects of prostaglandin synthesis inhibit drugs include sodium and fluid retention leading hypervolemia and hypertension, peptic ulceratio acute hypersensitivity interstitial nephritis, and acu renal failure, minimal lesion nephrotic syndrome, a hyperkalemia. Angiotensin converting enzyme inhibit drugs will reduce angiotensin II level and, consequent aldosterone level, thus will increase serum potassium lev Major side effects include low blood pressure, acute re failure, and hyperkalemia.

Liddle's Syndrome

Liddle's syndrome can be treated by one of the followi agents, alone or in combination.

1. K^+ supplement
2. Amiloride or triamterene

The preparations and dosage regimen for supplement, amiloride, and triamterene have be described. Spironolactone is not effective and should not be used.

Beta Blocker Therapy

Little information is available about the use of beta blocker therapy in the treatment of hypokalemia except familial periodic paralysis. Potential conditions for intracellular translocation of K are trauma, anxiety reaction with hyperventilation syndrome, and respiratory alkalosis. Any beta blocker drug may be used. Exact dosage is unknown. Atenolol was used successfully in the patient, which is presented here. (See Tables 7, 8, 9, and 10 and Fig. 5.)

Discharge Medications

1. Synthroid 388 mcg po daily
2. Prevacid 30 mg daily po daily
3. Magnesium oxide 400 mg po TID
4. Monthly B12 injections
5. Cymbalta (antidepressant) 60 mg po daily
6. Atenolol 12.5 mg po twice daily
7. Micro-K 8 mg po TID

A Special Mention about Primary Hyperaldosteronism

A patient is presented to illustrate an enigma in diagnosis and treatment of hypokalemia (see Table 11 and Figs 6 and 7).

Table 7. Unusual patient with recurrent hypokalemia diarrhea vs. RTA vs. familial periodic paralysis KN 73 WF admitted to a local hospital x 2

	Admission	*Discharge*
First	Oct. 19, 2008	Oct. 27, 2008
Second	Nov. 14, 2008	Nov. 26, 2008
Chief Complaints	Weakness and Tiredness; (2) Diarrhea for a long time.	
Past Medical History Significant for Hypokalemia	Gastric bypass surgery 20 years ago. No history of diabetes or hypertension. Steady Medications: Levothyroxin. Intermittently furosemide and potassium chloride intake until 2 months prior to first admission.	

HYPOKALEMIA IN PATIENTS WITH CHF

Treatment Consideration

1. The majority of patients with CHF are at increased risk for hypokalemia (diuretics use).
2. Potassium replacement should be routine in patients with CHF, even if serum potassium is normal (4 mmol/L).
3. In patients with CHF, mild to moderate hypokalemia can increase the risk of cardiac arrhythmias.

Magnesium Repletion and its Effect on Potassium Homeostasis in Critically Ill Adults

1. Hypomagnesemia is a frequent finding in hospitalized patients that occurs in approximately 65 percent of medical intensive care patients with normal serum creatinine concentrations.
2. Hypomagnesemia is often found concurrently with hypokalemia and hypochloremia.

Table 8. KN 73 y WF admissions

2008	*Oct 19th*	*Nov 14th*
Serum	Weakness of Lower Extremities	Profound Weakness of Lower Extremities, Inability to Move Her Legs
Na (mmol/L)	143	140
K (mmol/L)	2.1	1.8
Cl (mmol/L)	112	112
CO_2 (mmol/L)	17	13
BUN (mg/dL)	17	37
SCr (mg/dL)	2.07	2.87
eGFR (ml/min)	25	17
Glucose (mg/dL) (mmol/L)	78	77
Magnesium (mg/dL)	NA	1.2
Urine		
Na (mmol/L)	72/162	13
K (mmol/L)	2/2	4
NA = not available.		

Table 9. KN 73 y WF urinary anion gap Na^+ K – Cl

2008	*Oct 19th*	*Nov 14th*
	-7 mmol/L	+13 mmol/L

Table 10

2008 Nov - Dec								
Admission	20 mEq	D/C KCl	5 W č K+	D/C I/V	D/C	↓	Atenolol	Discharge
5% Dextrose	KCl	infusion	@ 50 c.c. /	fluid	Spironolactone	Atenolol	to 12.5 mg	Atenolol
w/20 mEq	PO TID.	PO free water	hr x 20 hr.	D5W č	D/C	to 12.5	PP	12.5 mg
KCl/L	Aldactone	1200 mL/24 hr	40 mEq K/Q	50	Amiloride	mg PO	BID	twice a day.
Discontinued	50 mg PO	KCl 60	4 hr PO	mmK.Phos-	↓ KCl to 20 mEq	TID	↓ KCl to	K-dur 20
next day	then	mEq/24 hr-	Aldactone	per liter	PO BID		10 mEq	mEq twice a
	25 mg PO TID	Spironolactone	50 mg QID	↑ Atenolol			PO twice	day
	Amiloride 5 mg	½ normal	Atenolol 25	12.5 mg PO			daily	
	BID	saline č 30	mg PO	6 hrs				
	½ normal	mmol	daily					
	saline	of K-Phosp	then					
	w/40 mEq KCL/L		12.5 mg PO					
	infusion		BID					

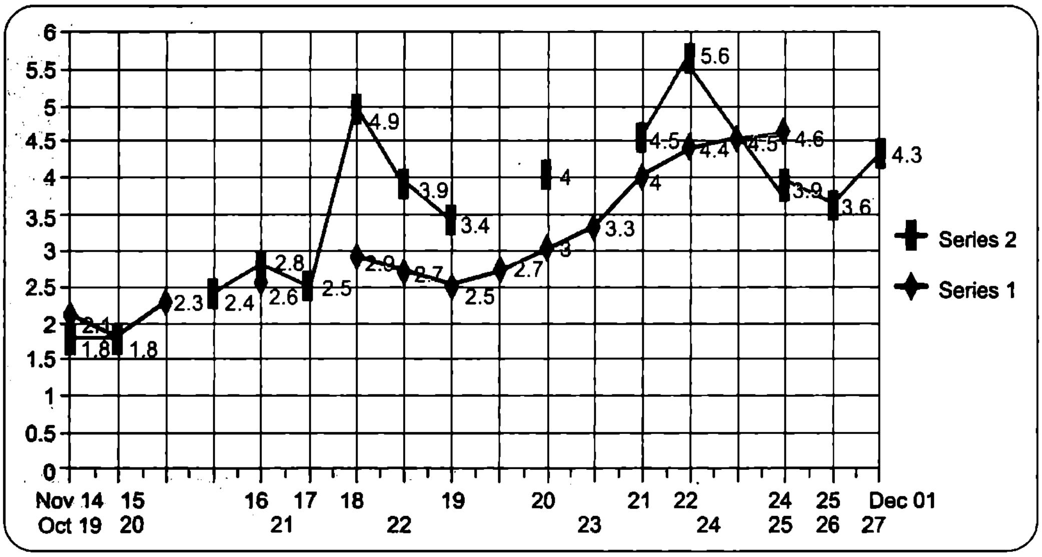


Figure 5: Management as daily medicines administered--potassium level in mmol/L

3. Magnesium repletion has been shown to facilitate correction of potassium and calcium deficiencies.
4. Administration of magnesium has been shown to decrease the risk of dysrhythmias and death after myocardial infarction by 25 percent to 74 percent.

Magnesium Supplementation/Preparation

1. Magnesium oxide 400 mg po TID if serum magnesiun >1.5 <1.8 mg/dL and not on diuretic therapy
2. Magnesium sulfate 50 percent solution, if serun magnesium is < 1.5 mg/dL, definitely if < 1 mg/dL an

Table 11. 68 y African-American female (nonsmoker/nondrinker, part-time employed)

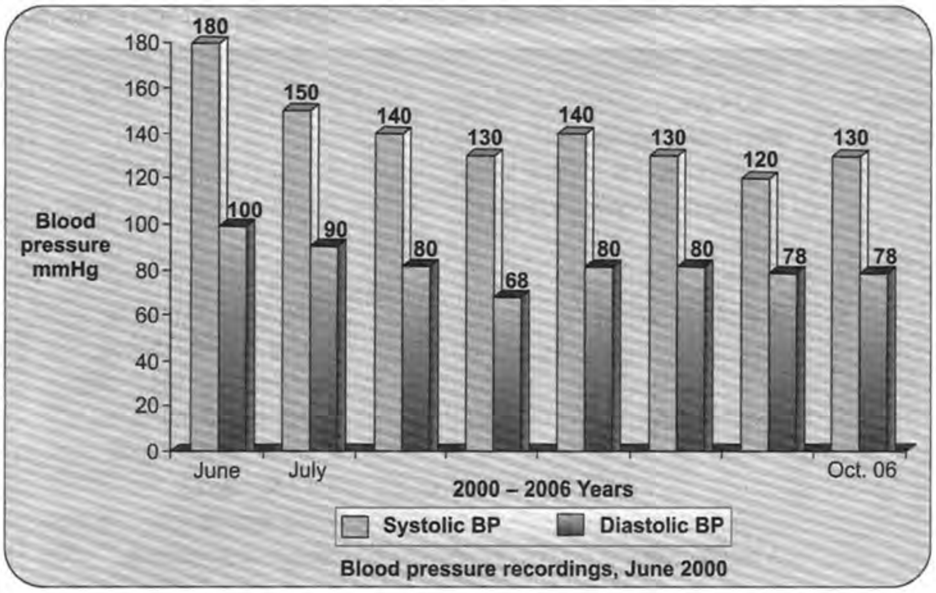
First office visit	June 29, 2000	
History of hypertension	13-14 yrs.	
Reason for referral:	Persistent hypokalemia	
Medication:	(1) Norvasc 10 mg once a day, (2) Naproxen now and then	
Diuretic Abuse:	None	
Laxative Abuse:	None	
Exam:	Blood pressure	Lying 180/100 mmHg Sitting 170/100 mmHg Standing 160/104 mmHg
Lab:	Feb 14, 2000	Glucose 155 mg/dL BUN/Cr 13/0.9 mg/dL Na 144 mmol/L K 3.4 mmol/L
	May 30, 2000	Serum K 3.1 mmol/L Urine K 22 mmol/L Creatinine clearance 67 ml/min
Initial Diagnosis:	Potassium secreting state High urinary K despite hypokalemia	
		Primary hyperaldosteronism Bartter's syndrome Liddle syndrome Gitelman's syndrome
	June 1, 2000	Ultrasound of kidney 1.5 cm cyst in right kidney
	Ordered:	Plasma renin activity Serum aldosterone Drug screening
Therapy:	↑ Norvasc 10 mg twice daily started spironolactone (Aldactone®) 25 mg po twice daily Δ Norvasc 5 mg BID Spironolactone 25 mg TID ↑ 37.5 mg QID	
	Oct 25, 2000	MRI of abdomen-right adrenal adenoma Serum aldosterone 27 ng/dL (n=0-31.9) Renin 3.40 ng/ml/h (n=< 3.4) Ratio: Aldo/Renin = 7.9

Cr = Serum Creatinine

patient has potential for cardiac arrhythmia. 2 ml (1g) IM every 8h × 6 doses. Intravenous magnesium does not sustain, as it is promptly excreted by the kidneys and also causes hypotension.

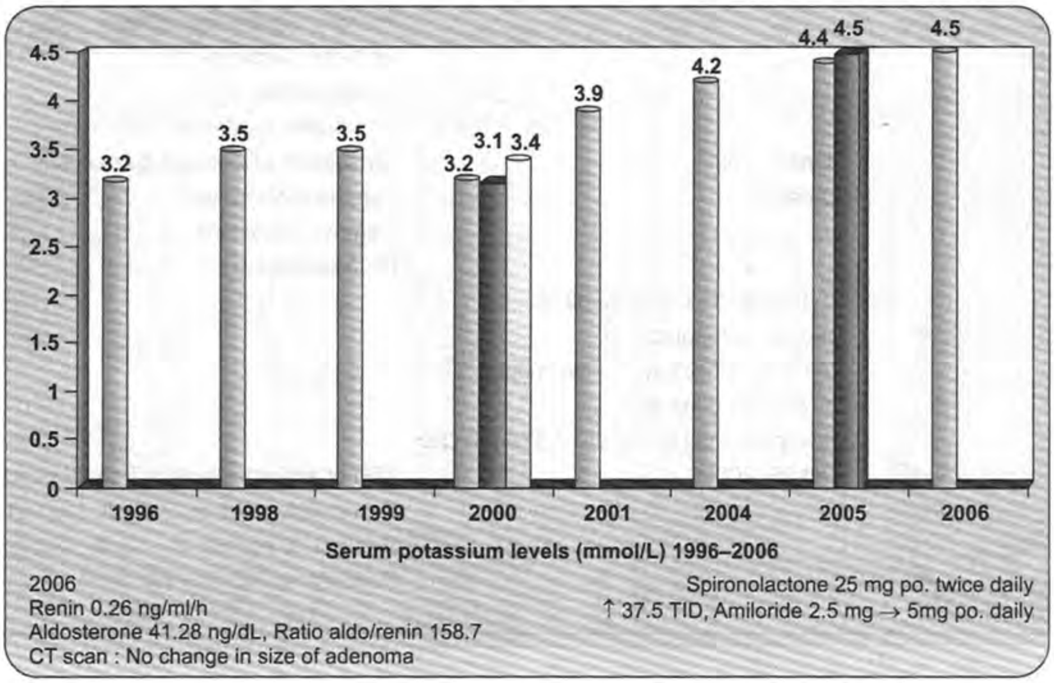
Adjuvant Therapy

Hypokalemia with severe metabolic alkalosis pH >7.55 to 7.6 as in severe vomiting or nasogastric suction.



Blood pressure recordings, June 2000

Figure 6: Blood pressures were uncontrolled, then with initiation of spironolactone therapy, blood pressures were controlled and maintained at normal level



Serum potassium levels (mmol/L) 1996–2006

2006
Renin 0.26 ng/ml/h
Aldosterone 41.28 ng/dL, Ratio aldo/renin 158.7
CT scan : No change in size of adenoma

Spironolactone 25 mg po. twice daily
↑ 37.5 TID, Amiloride 2.5 mg → 5mg po. daily

Figure 7: Serum potassium levels were low (<3.5 mmol/L) or low normal before initiation of spironolactone and amiloride in the year 2000. After initiation of spironolactone and amiloride, serum potassium became normal and stayed normal (>3.5 mmol/L)

1. Enhance bicarbonate excretion by using acetazolamide 500 mg IV × 4 doses then 250 mg po every 6h until pH ≤ 7.4.
2. H2 blocker or proton pump inhibitor to prever formation of HCO_3 in stomach and its absorption an prevent loss of K^+.

Prevention of Hypokalemia

In diuretic therapy: NG suction/Edematous condition

Measures Alone or in Combination, Depending on Serum K Level and Renal Function Status

1. KCl po 20 mEq twice daily
2. Potassium retaining agent such as amiloride 1.25 to 2.5 mg po twice daily
3. H2 blocker or proton pump inhibitor

KEY POINTS

1. Chronic diuretic therapy is the most common cause of hypokalemia in outpatient setting.
2. Postsurgery, intractable vomiting, continuous NG suction, or severe diarrhea are a common cause of severe hypokalemia in hospital setting.
3. Surreptitious vomiting, diuretic or laxative abuse is an obscure cause of hypokalemia.
4. Even mild hypokalemia can induce atrial or ventricular arrhythmia in patients with CHF, digitalis therapy or myocardial infarction.
5. Sudden death may occur even with mild hypokalemia in patients with CHF (Torsade de Pointes).
6. Oral potassium is the safest form of replacement; potassium chloride is the preparation of choice.
7. Intravenous K in saline vehicle (not dextrose) is indicated in cardiac arrhythmia, familial periodic paralysis or respiratory failure.
8. A potassium retaining agent is an essential additive in severe hypokalemia. Amiloride is the drug of choice.
9. Magnesium depletion often will cause renal potassium wasting, preventing potassium replacement from being effective. Magnesium supplementation is essential in hypomagnesemia.
10. KCl 20 mEq twice daily should be a routine in patients with diuretic therapy, CHF, MI, cirrhosis of liver, and edematous condition. Adjust dose according to renal function.

Helpful Tips in Treating Hypokalemia

Finally, some helpful tips are provided to facilitate treatment of hypokalemia. In edematous conditions, such as nephrotic syndrome, a perplexing situation sometimes arises in the management. Not infrequently after an initial good response, a diuretic does not produce diuresis as much as expected, even with normal renal function. It has been mentioned earlier that edematous patients promptly develop hypokalemia with diuretic therapy, suggesting a preexisting potassium depletion state. Increasing the dosage of diuretic or substituting one diuretic for another does not help. This diuretic-resistant state is apparently due to intracellular Na^+ and fluid retention, which can be averted by increasing the dosage of K^+ supplement and/or adding potassium sparing agent to the regimen. Large amount of potassium will cause efflux of intracellular Na^+, which will lead to natriuresis and, hence, enhance diuresis.

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6

Hyperkalemia: Pathophysiology, Diagnosis, Treatment, and Prevention

Anil K Man

INTRODUCTION

Hyperkalemia is not as common as hypokalemia. If all patients with acute and chronic renal failure are excluded, the incidence of hyperkalemia will be rather insignificant. At the outset, it should be stressed that hyperkalemia is often pseudo and caused by an abnormal technique in drawing the blood, extravascular hemolysis, or sharp change in ambient temperature. Less frequent causes of pseudohyperkalemia include leukocytosis, thrombocytosis, or in vitro contamination with K-EDTA in the sample collection tube. If hyperkalemia (>5 mmol/L) is observed as an incidental finding in the laboratory report of a patient who is otherwise asymptomatic, it is needless to become panicky. In an asymptomatic patient, hyperkalemia is most likely to be pseudohyperkalemia and probably is caused by hemolysis. If there is no evidence of hemolysis in the blood sample and white blood cell and platelet counts are normal, whole blood (plasma) should be analyzed for potassium. Plasma potassium should be normal in case of pseudoelevation of serum potassium.

Serum potassium level greater than 5.0 mmol/L is hyperkalemia. While mild hyperkalemia (5.0 to 5.5 mmol/L) is of slight concern, moderate (5.5 to 6.5 mmol/L) or severe (>6.5 mmol/L) hyperkalemia can lead to grave consequences. As stated in the chapter on hypokalemia, 80 to 85 percent of the daily potassium intake is excreted by the kidneys. Therefore, inability of the kidneys to secrete and excrete K^+ load in acute and chronic renal failure could result in retention of potassium and hyperkalemia. Interestingly, kidneys retain the ability to secrete and excrete potassium despite moderate to severe renal failure. This is especia true in patients with good urine output. Furthermo gastrointestinal tract excretes more potassium chronic renal failure than in normal condition. Thu severe hyperkalemia does not develop in patients wi uncomplicated chronic renal failure as often as o would expect. It should be noted, however, that t delicate potassium balance in chronic renal failu may be tipped off easily by potassium load caused indiscriminate intake of potassium in foods, or relea of tissue stores of potassium as a result of infectio trauma, or sharp decrease in kidney function. Imbalan in internal potassium homeostasis or inhibition potassium secretion as happens with use of certain dru can lead to hyperkalemia even in the presence of mi renal insufficiency.

True hyperkalemia can occur in any of the four maj categories of pathophysiology.

DECREASE IN K^+ EXCRETION

Potassium excretion will be reduced when (1) filtrati of potassium is decreased as a result of decrease glomerular filtration rate; and (2) secretion of potassiu is inhibited as a result of decreased mineralocorticoi

1. Potassium excretion is decreased in acute a chronic renal failure. Severe hyperkalemia occu more commonly in acute than stable chronic re failure. It is common especially in hypercatabo acute renal failure (ARF) and ARF associat with rhabdomyolysis or tumor-lysis syndrome. mentioned earlier, in stable chronic renal failu severe heperkalemia is rather uncommon, which m

be in part, due to high circulating aldosterone levels observed in chronic renal failure.

2. Secretion of potassium is inhibited in—
   a. Diffuse adrenocortical insufficiency or Addison's disease. In Addison's disease hyperkalemia is almost always accompanied by hyponatremia, hypovolemia, hypotension, especially postural hypotension, and renal insufficiency. In all cases of hyperkalemia, the possibility of Addison's disease should be considered. Aldosterone deficiency does not occur in adrenal insufficiency secondary to pituitary failure. Therefore, hyperkalemia is not a feature of secondary adrenal insufficiency.
   b. Selective hypoaldosteronism. Hyperkalemia is the hallmark of selective hypoaldosteronism. A serious cardiac arrhythmia or cardiac arrest due to hyperkalemia often draws attention to the problem. Hypoaldosteronism may be idiopathic or secondary to hyporeninemia. The syndrome of hyperkalemia, hypoaldosteronism, and mild to moderate renal insufficiency is usually due to a hypoplastic juxtaglomerular apparatus seen in diabetic nephropathy or any type of chronic tubulointerstitial nephritis.
   c. Drugs: Discrete groups of drugs that preferentially inhibit K^+ secretion include:
      i. Potassium-sparing drugs: spironolactone, triamterene, amiloride.
      ii. Prostaglandins synthesis inhibitors
      iii. Angiotensin converting enzyme inhibitors / angiotensin receptor blockers (ACEI/ARB)
      iv. Trimethoprim (Bactrim®)
      v. Beta-blocking drugs
      vi. Other drugs: Pentamidine, digitalis, calcineurin inhibitors, such as cyclosporine or tacrolimus and succinyl chloride

Potassium-sparing drugs have been described in the section on hypokalemia. The prostaglandin synthesis inhibitors and ACEI or ARB drugs diminish production of angiotensin II, and consequently aldosterone, thereby leading to inhibited potassium secretion.

INCREASE IN POTASSIUM LOAD (INCLUDES INTAKE)

The ability of the kidneys to excrete a potassium load is much slower than sodium load. It takes 6 hours to excrete 85 percent of a potassium load compared to 30 minutes to 1 hour for a sodium load with normal renal function. Excretion of potassium load may be greatly prolonged with reduced renal function. Thus, in patients with renal insufficiency, indiscriminate consumption of potassium-rich foods is a frequent cause of life-threatening hyperkalemia. Sudden death among maintenance hemodialysis patients has been attributed to noncompliance in diet and consequently hyperkalemia. In tumor-lysis syndrome and rhabdomyolysis, massive release of potassium occurs from the intracellular space to the extracellular space. However, hyperkalemia does not occur unless ARF supervenes. Similarly, trauma, intravascular hemolysis, transfusion of stored blood, and catabolic state, such as infection or high fever, can be associated with excessive release of potassium from the cells. Again, hyperkalemia usually does not develop in the presence of intact renal function and normal or high urine output.

Interesting Examples of Large Intake of Potassium

1. A 51-year-old man suddenly developed ascending symmetric paralysis. Serum potassium was 9 mmol/L. Marked elevation of serum potassium was due to intake of 2.5 liters of orange juice per day for 3 weeks. Potassium load was 1125 mmol of potassium per day for 3 weeks.
2. A 15-year-old girl ate a diet consisting of 20 bananas per day. Serum potassium on this diet varied from 4.7 to 6.1 mmol/L.
3. A 55-year-old woman admitted to self-medication of 500 ml of potassium citrate per day for dysuria. Her serum potassium was 9.6 mmol/L.

Tubular Unresponsiveness to Aldosterone

In certain conditions, namely sickle-cell anemia, systemic lupus erythematosus, amyloidosis and renal transplantation, hyperkalemia may occur due to a defect in the tubular secretion of potassium. This defect has been ascribed to tubular unresponsiveness to aldosterone, possibly due to a defect in the receptor binding of aldosterone. Plasma renin activity and plasma aldosterone levels are normal. Renal tubules respond to the administration of mineralocorticoids by retention of sodium and water but without the increase of potassium secretion or excretion. The mechanism of this unresponsiveness to aldosterone relative to potassium secretion is unknown.

REDISTRIBUTION OF POTASSIUM

Efflux of potassium from the intracellular space to the extracellular space can occur in a variety of conditions. This includes metabolic acidosis, such as in renal failure, diabetic ketoacidosis, lactic acidosis, digitalis overdosage, use of heparin, following infusion of arginine or lysine hydrochloride for the treatment of metabolic alkalosis or following infusion of hypertonic solution such as 3 percent sodium chloride solution, 50 percent dextrose or 25 percent mannitol. Hypertonic solution increases the osmolality of the extracellular space, which causes dryness of the cells and leakage of potassium from the intracellular space to the extracellular space. Like hypokalemic periodic paralysis, there is an entity called hyperkalemic periodic paralysis. This is due to efflux of potassium from intracellular space to the extracellular space. Finally, beta receptor blocking drug, e.g., propranolol can cause hyperkalemia by blocking the effect of epinephrine. Epinephrine causes translocation of K^+ from the extracellular space to the intracellular space. In renal failure with tendency to potassium retention and hyperkalemia, epinephrine subserves the protective function against hyperkalemia. If this protective function is blocked, as with use of beta blocker, extracellular hyperkalemia may occur readily. This may not occur with cardio-selective beta blocker, such as atenolol or metoprolol.

In summary, pseudohyperkalemia is far more common than true hyperkalemia. Life-threatening hyperkalemia does occur, most commonly in acute and chronic renal failure, especially in patients who indiscriminately consume potassium rich foods, use salt substitute or in those patients with inadvertent use of potassium-sparing agent, beta-blocking or ACEI drugs. Hyporeninemic hypoaldosteronism is recognized increasingly as a cause of alarming hyperkalemia among elderly, diabetics or patients with advanced vascular disease or some type of chronic tubulointerstitial disease (type IV RTA). Addison's disease should be suspected in all patients with obscure hyperkalemia.

OTHER CAUSES OF HYPERKALEMIA

Anastomosis of the ureters into the jejunum can cause hyperkalemia, because jejunum reabsorps potassium. Anastomosis of the ureters into the ileum causes hypokalemia.

A 77-year-old man underwent extensive pelvic surgery for rectal carcinoma. Because of multiple pelvic adhesions the ureters were inadvertently diverted into jejunum Upon initiation of enteral feedings, which contains high potassium, he developed hyperkalemia.

Recapitulation of Drug-induced Hyperkalemia

Drug-induced hyperkalemia is recognized at an increased rate. The most common group of drugs in that regard is renin-angiotensin inhibitor drugs.

Impaired renal function is the fundamental pathophysiologic basis of drug-induced hyperkalemia. Lower the renal function, higher is the risk of drug-induced hyperkalemia. ACEI drugs, such as lisinopril, ramipril, or quinapril, and angiotensin receptor blocking drugs, such as losartan or valsartan, top the list of drug-induced hyperkalemia in current practice of medicine. The reasons for high incidence of hyperkalemia caused by these drugs are attributable to:

1. These drugs predictably decrease renal function, especially in elderly subjects, in those with uncontrolled diabetes, and in those with preexisting renal failure.
2. These drugs decrease hydrogen ion secretion by decreasing aldosterone production, giving rise to metabolic acidosis. Hydrogen ion is buffered in the intracellular space with efflux of potassium from intracellular space into extracellular space.

Here are some data to that effect: 119 patients were treated with ACEI; 46 of 119 (38 percent) developed hyperkalemia. Serum potassium ranged from 5.2 to 6.7 mmol/L with a mean potassium of 5.68 ± 0.3 mmol/L. Of these patients with hyperkalemia, 96 percent had chronic renal failure, 84 percent had diabetes, and 30 percent congestive heart failure (CHF).

A 59-year-old African-American male with a long history of diabetes was admitted to a hospital with diagnosis of ARF, hyperkalemia, and metabolic acidosis. He was taking lisinopril 20 mg orally daily. Lisinopril was discontinued, and he was treated with insulin, and normal saline with sodium bicarbonate infusion. His glucose control improved, and renal function returned to normal as did the electrolytes and acid-base balance. The results are shown in Table 1.

Here is an analysis of drug-induced hyperkalemia from Putnam Community Medical Center, Palatka, Florida, in 2008 with ICD code of hyperkalemia.

Total number of patients 17			
M:F 7:10			
Serial potassium levels (mmol/L)			
Upper range 5.0 to 9.1		Lower range 4.9 to 6.0	
Mean: 6.2		Mean: 5.2	
Renal Function			
	BUN (mg/dL)	Serum creatinine (mg/dL)	eGFR (ml/min)
Upper Mean	59.6	3.5	28.2
Lower Mean	41.6	2.2	38.5

Drugs used in these 17 patients: Digoxin*7; lisinopril 4; spironolactone 4; bactrim* 2; naproxen 2; losartan 2; telmisartan 1; potassium 1; enalapril 1; benazepril 1; irbesartan 1. Total number of patients who took ACEI/ARB were 10 (59 percent). Therefore, ACEI/ARB are the cause of hyperkalemia in greater number of hospitalized patients. Of these 17 patients, 12 had CHF with renal insufficiency and 5 patients had hypertension and diabetes.

A study has shown that severe hyperkalemia is associated with renal failure in 75 percent of the cases, and a predisposing drug was found in 67 percent of the cases.

Aldosterone synthase deficiency is characterized by hypovolemia, hyponatremia, and hyperkalemia.

DIAGNOSIS OF HYPERKALEMIA

Clinical manifestations of hyperkalemia are fewer but more severe than those of hypokalemia. Sometimes a patient is brought to the emergency room with a history of severe chest pain resembling acute myocardial infarction or because the patient had cardiac arrest. Muscular weakness and paresthesias in the hands and feet are not uncommon complaints. Hyperkalemic periodic paralysis may occur. Usually there is a history of diabetes, hypertension, or chronic renal disease or the use of one or more of the drugs already stated.

The electrocardiogram is most rewarding. The changes consist of:

1. Tall peaked T wave (>5 mm) with serum K^+ level, 6 to 7 mmol/L.
2. Widening of QRS complex and smaller amplitude of P wave with serum K^+ level, 7 to 8 mmol/L.
3. QRS complex merges with T wave forming sine waves with serum K^+ level, 8 to 9 mmol/L.
4. When serum K^+ level increases more than 9 mmol/L atrioventricular dissociation, ventricular tachycardia or ventricular fibrillation and death may ensue. Most of these patients will almost invariably show concomitantly moderate to severe azotemia and moderate to severe metabolic acidosis.

In tumor-lysis syndrome and rhabdomyolysis, other concomitant features include hyperuricemia and hyperphosphatemia. Hypocalcemia occurs in some patients.

Diagnosis of the Etiology of Hyperkalemia

In all patients with hyperkalemia, especially in those with recurrent or chronic hyperkalemia, investigations must be done to determine the cause of hyperkalemia. The following are stressed:

1. History of intake of salt substitute (contains KCl and NH_4Cl), potassium supplement, potassium-sparing agent, beta-blocking agent, ACEI or nonsteroidal anti-inflammatory drugs (prostaglandin synthesis inhibitors).

Table 1. 59 AAM serial laboratory studies

Date 2005	*Glucose (F) (mg/dL)*	*BUN (mg/dL)*	*SCr (mg/dL)*	*Na^+ (mmol/L)*	*K^+ (mmol/L)*	*CO_2 (mmol/L)*
August 18	302	76	7.4	126	5.9	15
Hospital admission: Lisinopril discontinued						
August 19	274	80	8.2	127	5.0	17
Normal saline with 3 ampoules of sodium bicarbonate infusion per liter bag at 60 ml/hour started						
August 20	249	68	2.2	133	5.6	18
August 21	196	22	0.8	139	4.2	32
August 22	186	10	0.8	140	3.8	33
Discharged from the hospital						

2. In patients with mild hyperkalemia, especially those with hyponatremia and postural hypotension, a morning (6 am) serum cortisol level should be obtained. If this serum cortisol level is low (N = 7 to 25 ug/dL) (serum cortisol level is highest in early morning specimen), cortisone stimulation test should be done. Cortisone stimulation test can be done by infusion of 50 units of adrenocorticotropic (ACTH) in a liter of saline continuously for 8 hours and measure the serum cortisol level after completion of infusion. The alternative choice will be to inject synthetic ACTH analogue (Cortrosyn®) 0.25 mg subcutaneously and measure serum cortisol level before and 30 minutes after Cortrosyn®. In either test a normal individual shows increase in plasma cortisol level by at least 10 ug/dL from the baseline level. A patient with Addison's disease shows no or slight elevation in plasma cortisol level after ACTH challenge.
3. In patients with long history of diabetes mellitus, or history suggestive of some type of tubulointerstitial renal disease, plasma renin activity and plasma aldosterone level should be obtained.

MANAGEMENT OF HYPERKALEMIA

1. Mild to Moderate Hyperkalemia (serum K$^+$ 5.0 to 6.5 mmol/L): Recommended therapy includes the following:
   a. Low-potassium diet (50 to 60 mEq/day)
   b. Avoid or discontinue salt substitute, potassium supplement, potassium-sparing agent, heparin, beta-blocking agent, ACEI/ARB group of drugs or nonsteroidal anti-inflammatory drugs. If a patient is hypertensive, treat hypertension with clonidine, hydralazine, alpha blocker or calcium channel blocker. Beta blocker is not safe in these patients.
   c. Use sodium polystyrene sulfonate (Kayexalate®) (Winthrop-Breon). This agent is a cation exchange resin; in vivo, 1 gm of the resin exchanges 1 mmol Na$^+$ for 1 mmol K$^+$ per liter in the intestines. It can be given orally or rectally. Oral route is more effective than rectal (enema) because it traverses throughout the intestines and produces much larger exchange of potassium than when administered as enema. Following oral administration, sodium is released from the resin in exchange for hydrogen ions in the acidic environment of the stomach. As the resins passes through the intestines, hydrogen cations exchange with those cations that are in greater concentration and the cationically modified resin is excreted in the feces. Because of the relatively high concentration of potassium present in the large intestine, conversion of the resin to the potassium form occurs principally in the large intestines. Following rectal administration, sodium ions are partially released from the resin in exchange for other cations present.

Kayexalate® is available in the powder form or as a suspension.

Kayexalate® is suspended in 30 percent sorbitol and provides 5 gm in 20 ml suspension. The recommended oral dose in severe hyperkalemia is 15 to 30 ml 4 times daily or until serum potassium level is around 5 mmol/L. Then it should be given as a maintenance dose of 5 ml 2 times daily. Kayexalate® given in powder form can produce anorexia, nausea, vomiting and constipation. The latter is most troublesome, especially in elderly patients. However, most of these symptoms are alleviated by suspending Kayexalate® in 30 percent sorbitol. In those with diabetes, sorbitol may markedly increase glucose Therefore, in patients with diabetes, Kayexalate powder will be given mixed with water.

If oral administration is not tolerated, sodium polystyrene sulfonate may be administered rectally as a retention enema. Sixty to one hundred gram of Kayexalate® powder can be administered after it is suspended in 100 to 200 m vehicle, such as 30 percent sorbitol or 10 percen dextrose and warmed up to body temperature Alternatively, 120 to 180 ml of the commerciall available suspension may be administered a a retention enema, after the suspension ha been warmed up to body temperature. After a initial cleansing enema, a soft, large (French 28 rubber tube should be inserted about 20 cm int the rectum, and taped in place. The Kayexalat suspension is then administered rectally b gravity. The tube may then be flushed with 50 100 ml of normal saline, clamped and left in plac If back leakage occurs, the patient's back shou be elevated. The suspension may be retained for 60 minutes or for several hours, after which the rectum is washed with normal saline.

d. For metabolic acidosis which is a concomitant feature of hyperkalemia, administration of sodium bicarbonate or sodium citrate (citrate is converted into bicarbonate in the body) is recommended. Sodium bicarbonate 650 mg tablet 2 or 3 times daily or mixture of sodium citrate and citric acid (Shohl's solution) should be prescribed. Shohl's solution is tasteful. One ml of Shohl's solution contains 1 mEq Na^+ and citrate after metabolic degradation will produce 1 mEq HCO_3. The usual dose is 10 to 15 ml 3 times daily. Care must be taken in not overloading the patient with Na^+ which will lead to hypervolemia, hypertension and possible CHF. The problem of Na^+ retention, however, may be minimized by the concomitant use of a loop diuretic, if the patient has some residual renal function. Excessive use of Shohl's solution may lead to metabolic alkalosis and hypocalcemia. Additionally, sodium citrate is an anticoagulant which increases the propensity to bleeding in uremia. Shohl's solution should not be administered with aluminum hydroxide gel as aluminum absorption may be enhanced.

2. *Severe hyperkalemia (serum K^+ >6.5 mmol/L):* Wide QRS complex, sine waves or ventricular tachycardia in the electrocardiogram is regarded as an emergency. It should be mentioned, however, that serum potassium level alone is not the sole determining factor for the cardiotoxicity effect. Management in this emergency is discrete and explicit, and should be done in rapidly successive fashion and in the following order:

   a. Calcium Gluconate: It is available as 10 percent solution in 10 ml ampoule (1 ml contains 0.48 gm calcium). Twenty ml must be pushed intravenously directly in 5 to 10 minutes and the doses may be repeated after 1 to 2 minutes, if necessary. Calcium antagonizes the membrane excitability induced by hyperkalemia and abolishes the ventricular arrhythmias. It should be remembered, however, that calcium does not lower serum K^+ level. The action of calcium is immediate, however, it lasts for a few minutes. Therefore, intravenous push should be followed by a calcium infusion in which 5 ampoules are added into a 500 ml bottle of 10 percent dextrose or 5 percent dextrose and normal saline solution and infused slowly.

   b. Sodium Bicarbonate Infusion: It is available as 7.5 percent solution (44.6 mEq) in 50 ml ampoule, and 5 percent solution in 500 ml (297.5 mEq) bag. Two ampoules of sodium bicarbonate (100 ml) are given as direct intravenous push in 10 to 20 minutes (5 to 10 ml/min) followed by slow infusion from a 500 ml bag (2 to 4 ml/min). Sodium bicarbonate will combat metabolic acidosis and enhance intracellular translocation of K^+. Thereby serum K^+ level will decrease rapidly. It should be noted that sodium bicarbonate in the form of bolus or infusion is not as helpful for hyperkalemia in dialysis patients as it is in nondialysis patients.

   c. Glucose and Insulin: Glucose can be infused as a 10 percent solution 100 ml/hour for 2 hours along with 10 units of regular insulin for each 10 g glucose (100 ml 10 percent glucose solution contains 10 g glucose). Insulin will promote intracellular influx of potassium. Fifty percent glucose is less desirable in patients with some amount of renal function as such a hypertonic solution may produce dryness of cells and promote leaking of potassium from the cells. This may result in rebound hyperkalemia. Glucose and insulin therapy is very effective for treating hyperkalemia in dialysis patients.

   d. Dialysis Therapy: Once the threat of cardiac arrest has subsided, arrangement should be made immediately for hemodialysis with no or 1 mEq/L potassium in bath.

   e. Sodium Polystyrene Sulfonate: In the event facility for dialysis therapy does not exist or the patient has to be transported to a great distance for dialysis, treatment with Kayexalate® in sorbitol must be initiated immediately. In severe hyperkalemia, recommended initial oral dose is 60 ml, then 40 ml every 6 hours until serum K^+ is less than 6 mmol/L, then 20 ml 3 times daily. Excessive amount of sorbitol will cause diarrhea, which will further enhance K+ excretion. Kayexalate® also may be administered as a retention enema. This has been described already in detail.

3. Hypoaldosteronism: Hyperkalemia tends to be chronic and recurrent in selective hypoaldosteronism or hyporeninemic hypoaldosteronism. This chronic hyperkalemia in hypoaldosteronism may be treated by Kayexalate®, alkali as well as furosemide, but most effectively by 9-alpha-fluorohydrocortisone, a synthetic analog of aldosterone. The brand name is Florinef® (Squibb). It is available as 0.1 mg tablet. The usual dose is .05 mg to 0.5 mg daily. It is appropriate to begin with the smallest dose and gradually increase to a maximum dose of 0.5 mg daily monitored by regular examination of blood pressure (BP) and body weight. The drug is administered once daily.
4. Albuterol: Adrenergic agonist (albuterol or epinephrine) is very effective in translocating potassium rapidly into intracellular space and lowering serum potassium levels. Albuterol is safer than epinephrine from cardiac standpoint and can be given as 10 to 20 mg by nebulizer or 0.5 mg intravenously. Albuterol in combination with glucose and insulin has shown to lower serum potassium fast in dialysis patients.
5. If Addison's disease is confirmed, treatment should be initiated with hydrocortisone 37.5 mg daily. The total dose may be divided into 30 mg in the morning and 7.5 mg in the evening.

Prevention of Chronic or Recurrent Hyperkalemia

Largely Preventable: How?

1. Must avoid drug(s) that have caused hyperkalemia in the first place.
2. Diet control - Low-potassium diet: Restriction of intake of fruits, fruit juice, vegetables, and meat.
3. Caution in using beta blockers such as propranolol or atenolol in patients with renal insufficiency.
4. Avoid use of nonsteroidal anti-inflammatory drugs.
5. If hyperkalemia is just due to acute or chronic renal failure, one or more of the following therapies is recommended:
    a. Florinef® 0.1 to 0.2 mg PO daily (BP may increase, edema may develop)
    b. Concomitant furosemide to mitigate the above side effects
    c. Kayexalate® 5g in 20 ml sorbitol, or mixed with water for those with diabetes once or twice daily
    d. Hydrocortisone 25 to 37.5 mg PO daily in case of adrenal insufficiency.

KEY POINTS

1. A normal plasma (whole blood) potassium in the presence of elevated serum potassium concentration confirms the diagnosis of pseudohyperkalemia.
2. Review of medication list is essential to determine the cause of hyperkalemia.
3. Drug-induced hyperkalemia is the most common cause of hyperkalemia of all severity in current medical practice.
4. Renin-angiotensin-aldosterone inhibition group of therapy is the most common culprit of all the drugs.
5. Patients at greatest risk for ACEI-induced hyperkalemia are elderly subjects, those with uncontrolled diabetes, and those with renal insufficiency.
6. Adding an aldosterone antagonist, such as spironolactone, to ACEI in CHF dramatically increases the risk of life-threatening hyperkalemia.
7. Hyperkalemia is largely a preventive disorder by paying full attention to medication, diet, and sometime taking low dose Kayexalate® or fludrocortisone (Florinef®).

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7

Metabolic Acidosis and Metabolic Alkalosis

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INTRODUCTION

Maintenance of the acidity of body fluids within a narrow range is essential for proper functioning of various organs. Changes in blood pH to below 6.9 or above 7.9 are dangerous for survival. The fine balance of blood pH can be disturbed by abnormality of production, buffering or excretion of acid. Hydrogen ion is extremely reactive and affects many molecules which participate in vital physiological processes. Buffer systems minimize changes in blood pH by adjusting to changes in the hydrogen ion concentration.

There are several buffer systems to defend against changes in pH:

1. HCO_3-buffer system, which is the primary ECF buffer
2. Protein buffer system, which is the primary ICF buffer and also buffers ECF
3. Phosphate buffer system
4. Hemoglobin buffer system

CO_2 and bicarbonate mixture is the main buffer system. CO_2 acts as an acid and forms carbonic acid when it dissolves in water, donating hydrogen ions when they are needed. HCO_3 is a base, binding hydrogen ions when there are too many of them. The HCO_3^-/CO_2 buffer system reacts rapidly to changes in hydrogen ions.

$$H^+ + HCO_3^- \leftrightarrow H_2CO_3 \leftrightarrow CO_2 + H_2O$$

The hydrogen ion concentration of blood (H^+) is closely related to partial pressure of carbon dioxide (pCO_2) and bicarbonate concentration in blood, as shown by **Henderson-Hasselbalch Equation:** $pH = 6.1 + \log [HCO_3^-]/0.03\ pCO_2$.

Where 6.1 is the pKa (negative log of the aci dissociation constant) for H_2CO_3 and 0.03, the facto which relates pCO_2 to the amount of dissolved CO_2 i the plasma.

Kassirer-Bleich equation states that:

$$H^+ = 24.\ pCO_2/HCO_3$$

The pH of blood is expressed as negative logarithm o H^+. The normal concentration of H^+ in blood is about 4 nanoequivalents per liter (range 36 to 44 neq/L), whic is equal to the pH of 7.4. In the pH range of 7.2 to 7.5, th H^+ changes by 10 neq per liter for every 0.1 change in pH A rise in pH reflects a lower concentration of hydroge ions (alkalemia), and vice versa. The pathologic proces resulting in an increase in the H^+ is called acidosis, an the process resulting in a decrease in the hydrogen io concentration is called alkalosis. While acidosis is likel to cause acidemia, it is not essential, since the net amoun of hydrogen ions can be high, low or normal due to co-existent acidosis and alkalosis.

PRODUCTION OF METABOLIC ACIDOSIS

Metabolism of carbohydrates and fat produces abou 15,000 mmol/day of the volatile carbonic acid. Almos all of the carbonic acid is removed by the lungs, a a gas (CO_2). Metabolic acidosis is characterized b accumulation of fixed acid, which causes a decline i bicarbonate concentration. Respiratory compensatio to the acid accumulation increases ventilation, lowerin the pCO_2, bringing the pH towards normal value.

Endogenous acid production is defined as the amoun of fixed (nonvolatile), noncarbonic acid produced b cellular metabolism of sulfur-containing amino acids (cysteine, methionine), cationic amino acids (arginine, lysine), hydrolysis of dietary phosphate and incomplete metabolism of glucose and fatty acids into lactic acid and ketoacids. A typical North American adult diet results in 1 to 2 mEq/kg of fixed acid (such as sulfuric acid, phosphoric acid, etc.). In the extracellular fluid (ECF), this fixed acid titrates an equivalent amount of bicarbonate (HCO_3^-). The carbonic acid that is formed then dissociates into carbon dioxide (CO_2) and water (H_2O) and fixed acid anion (A^-). A^- is filtered and excreted by the kidneys as ammonium (NH_4^+) and titratable acid (TA).

Metabolic acidosis occurs as a result of a marked increase in endogenous acid production (e.g., lactic acidosis, ketoacidosis), loss of HCO_3^- stores (diarrhea or renal tubular acidosis), or progressive accumulation of endogenous acids in the setting of renal insufficiency. In the compensated state of metabolic acidosis, the arterial blood pH is lower than normal (acidemia), the serum HCO_3^- is lower than normal, and there is a compensatory decrease in the $PaCO_2$. It can also present with a normal pH and serum HCO_3^-, in the presence of a mixed acid-base disorder. The anion gap is a useful way of evaluating metabolic acidosis.

The Anion Gap

The evaluation of metabolic acidosis must include the determination of the anion gap (AG). It is defined as the difference between unmeasured anions (anionic proteins (albumin), phosphate, sulfate, organic anions) and unmeasured cations normally present in serum. Unmeasured anions (UA) - unmeasured cations (UC) = anion gap.

AG is calculated as follows:

$$AG = Na^+ - (Cl^- + HCO_3^-) = 10\text{-}12 \text{ mEq/L}$$

The formula above can be rewritten, using the unmeasured cations (UC), and the unmeasured anions (UA), as follows:

$$(UC) + Na^+ = (UA) + (Cl^- + HCO_3^-)$$

Thus,

$$AG = Na^+ - (Cl^- + HCO_3^-) = UA - UC,$$

Now it becomes apparent that an increase in AG can occur by a decrease in UC or an increase in UA. For example, AG may increase as a result of an increase in anionic albumin (which can be a result of either increased albumin concentration or increased serum pH). As a general rule, AG falls by 2.5 mEq/L for every 1 gm/dL decrease in total albumin concentration. Either a decrease in UA (e.g., albumin) or an increase in UC (Ca^{2+}, Mg^{2+}, K^+) causes decrease in AG. Addition to the blood of UC (e.g., Li^+) or cationic immunoglobulins (e.g., in plasma cell dyscrasias) also results in a decrease in AG. That is why a decrease in AG may be a clue to a diagnosis of multiple myeloma. A falsely low AG may be "created" by pseudohyponatremia (e.g., hyperviscosity, hyperglycemia and hyperlipidemia), or pseudohyperchloremia (e.g., bromide intoxication).

If the serum albumin is normal, increase in AG usually occurs as a result of addition to the blood of nonchloride-containing acids. A^- in these situations may be inorganic (phosphate, sulfate), organic (ketoacids, lactate), or exogenous (salicylate or ingested toxins which result in organic acid production). Addition of the new A^- to the blood does not alter the Cl^- concentration; thus the AG increases.

Respiratory Compensation for Metabolic Acidosis

A primary decrease in the plasma HCO_3^- concentration stimulates the chemoreceptors in the medulla, to cause a compensatory increase in the minute-ventilation. This results in a lower P_aCO_2 (hypocapnia), thus reducing the decline in pH. In a simple form of metabolic acidosis, the expected decline in P_aCO_2 can be calculated using the following formula:

$$\Delta P_aCO_2 = 1.2 \times \Delta HCO_3^-$$

Also,

$$P_aCO_2 = 1.5 \times HCO_3^- + 8 \pm 2$$

Another approximation can be given by P_aCO_2 = digits to the right of decimal in pH. Deviations from the anticipated value have the significance of a co-existent acid-base disorder.

Renal Response to Metabolic Acidosis

There are three mechanisms by which the kidneys can regulate plasma HCO_3:

1. Reabsorption of filtered HCO_3^-,
2. Excretion of TA,
3. Synthesis and excretion of NH_4^+.

Net Acid Excretion (NAE) is defined by $NAE = NH_4^+ + TA - HCO_3^-$. Approximately 80 to 90 percent of the filtered HCO_3^- is reabsorbed in the proximal tubule, with the remainder being reclaimed in the distal nephron. An amount of acid equal to the daily endogenous acid production must be secreted, in order to prevent metabolic acidosis. When renal function is normal, the kidneys respond to chronic metabolic acidosis by increasing NH_4^+ production/ excretion. This production/excretion is impaired in chronic renal failure, hyperkalemia, and renal tubular acidosis (RTA).

Urine anion gap, defined as $(U_{Na} + U_K) - U_{Cl}$, is used to indirectly estimate the urinary NH_4^+ excretion. Direct urinary NH_4^+ measurement is possible but is technically difficult to perform and is not readily available. In metabolic acidosis of nonrenal origin (e.g. diarrhea), the expected response by the kidney is to increase NH_4^+ production. This will result in an increase in Cl^- concentration, which will exceed the sum of $(Na^+ + K^+)$. The urinary anion gap will then be a negative value. In contrast, when the kidneys cause a metabolic acidosis by failing to excrete acid at a normal rate (in RTA), urinary NH_4^+ is quite low, resulting in a positive urinary anion gap. This inappropriate renal response to the metabolic acidosis is due to impaired ammoniagenesis or a tubular defect in H^+ secretion. Large positive urinary anion gaps can also be noted in the presence of ketones, drug anions, and toxins such as toluene metabolites in urine. In all these instances, the method would not be valid in differentiating a renal versus nonrenal cause of acidosis.

Systemic Effects of Metabolic Acidosis

Depending upon the rate and severity of its development, metabolic acidosis may be totally asymptomatic, or be associated with various life-threatening illnesses. Left untreated, it can lead to severe hemodynamic and metabolic consequences. The features of underlying disease causing metabolic acidosis compound clinical features of metabolic acidosis.

It is well known that a lower pH may cause arterial vasodilatation, decreased cardiac inotropism, increased incidence of cardiac arrhythmia, and decreased vascular responsiveness to intravenous vasopressor drugs. Acidosis, however, has a beneficial effect on tissue oxygenation due to improved dissociation of oxygen from hemoglobin. Hyperpnea and tachypnea (Kussmaul's respiration) can develop if the acidosis is acute and severe.

Inorganic acidoses (e.g., infusion of HCl), cause an increase in serum potassium levels whereas organic acidoses (e.g. lactic acidosis, ketoacidosis) do not affect the potassium levels as much. The largest buffering system in the body is the skeleton. Continuous buffering of excess circulating protons may lead to osteopenia, hypercalciuria, even nephrolithiasis or nephrocalcinosis. Metabolic acidosis inhibits protein synthesis, and accelerates protein and amino acid degradation, thus resulting in a negative nitrogen balance. Renal ammoniagenesis is stimulated in an effort to excrete the excess acid by increasing the formation of ammonia buffer. Careful evaluation and management of metabolic acidosis is extremely important in the care of complex medical patients.

High Anion Gap Metabolic Acidosis

Figure 1 below shows an algorithm for evaluation of metabolic acidosis. The differential diagnosis of metabolic acidosis with excess anion gap is generally straightforward. The history, physical exam, arterial blood gases, serum electrolytes, serum ketones, arterial lactate level, osmolality, and urinalysis are usually required to make a preliminary diagnosis and initiate appropriate treatment. These tests can confirm or rule out the five disorders that can cause a high anion gap acidosis. These disorders are: (1) renal failure (uremic acidosis), (2) L-lactic acidosis, (3) ketoacidosis, (4) toxin-induced acidosis (methanol/ ethylene glycol ingestion, and salicylate overdosage) and (5) D-lactic acidosis, from gastrointestinal overproduction.

Renal Failure

Renal failure can be associated with either a high anion gap or normal anion gap acidosis. The magnitude of the acidosis correlates with the level of GFR. Early in renal failure, there may be a hyperchloremic, nonanion gap, metabolic acidosis, which later leads to high anion gap metabolic acidosis. The elevated anion gap is the result of retention of acid anions (e.g., phosphates and sulfates) as the GFR declines. Also, as the renal failure progresses, there is less production and excretion of NH_4^+, as a result of decreased renal mass. The serum HCO_3^- generally ranges from 15 to 20 mEq/L; values less than 10 mEq/L may occur, however, with an anion gap as high as 30 mEq/L. The bones at the expense of bone demineralization and negative calcium balance buffer the retained acid.

In chronic kidney disease metabolic acidosis is treated with oral bicarbonate therapy to maintain the HCO_3^- concentration above 20 mEq/L. Initial daily

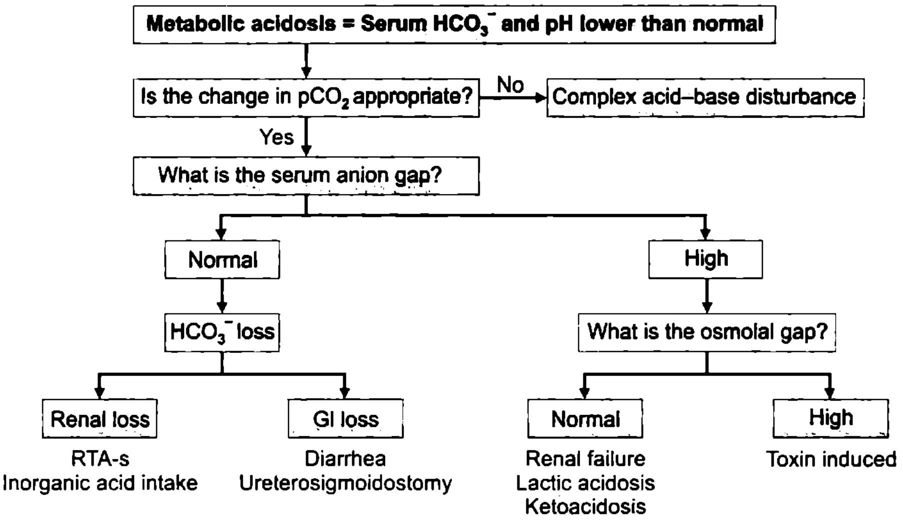

Figure 1: A simplified algorithm to differentiate common causes of metabolic acidosis

requirements may be higher, based on the bicarbonate deficit in select patients with long standing renal insufficiency. Maintenance dose of $NaHCO_3$ in a dose less than or equal to daily endogenous acid production should eventually be sufficient, once the serum HCO_3^- level returns to normal range. Either sodium bicarbonate tablets or sodium citrate (Bicitra) may be used. Citrate containing solution should not be administered to a patient receiving aluminum containing antacids, as it will markedly increase gastrointestinal absorption of aluminum and result in aluminum intoxication.

L-Lactic Acidosis

Approximately 1400 mmol of lactic acid is produced everyday in tissues from glucose. This is buffered by bicarbonate to form sodium lactate, which in turn is converted back to bicarbonate in liver. The kidneys metabolize only 10 to 20 percent of the tissue lactate. L-lactic acidosis is the result of overproduction or underutilization.

Type A lactic acidosis results from tissue ischemia due to impaired circulation, poor pulmonary function or low oxygen carrying capacity. Nonischemic **(type B)** lactic acidosis develops in patients with malignancies (especially leukemia) due to tumor or leukocyte overproduction of lactic acid; enzymatic defects such as glycogen storage diseases); certain drugs or toxins such as metformin, nucleoside analogues for HIV, and liver disease. Metformin is generally contraindicated in patients with GFR less than 60 mL/min or serum creatinine greater than 1.5 mg/dL. Type A L-lactic acidosis is the most common form and is commonly seen after cardiac arrest, in ischemic limbs or gut, cardiogenic shock, hemorrhage and sepsis.

The initial treatment of L-lactic acidosis should always be aimed at correcting the primary cause. It is critical to attempt to restore tissue perfusion as fast as possible when it is not adequate. Intravenous agents that cause vasoconstriction should be used cautiously, since they can worsen the tissue hypoperfusion. Treatment with alkali is recommended for acute, severe acidosis (pH < 7.1), in order to improve inotropism and response to vasopressors. The traditional use of $NaHCO_3$ is often considered controversial, mostly because it has not been clearly shown to improve the outcome and often results in excessive volume administration. An isotonic solution of $NaHCO_3$ is made by adding 3 ampules of $NaHCO_3$ (50 mEq/50 mL) to 850 mL of 5 percent dextrose in water (D5W). Other buffering agents have been used for correction of L-lactic acidosis. Dichloroacetate (DCA) stimulates the enzyme pyruvate dehydrogenase. Carbicarb® is an equimolar solution of $NaHCO_3$ and Na_2CO_3 and may result in less of an increase in P_aCO_2. THAM is a H^+ and CO_2 scavenger and can correct both metabolic and respiratory acidosis. To date, no studies have established the clinical advantage of any of these agents as compared to $NaHCO_3$. When using intravenous alkali therapy, once the primary cause of L-lactic acidosis has been corrected, it is possible to find an overshoot alkalosis, since the lactate is converted back to bicarbonate. Consequently, the target pH should generally be 7.20 to 7.25. For hemodynamically unstable, critically ill patients, there may be a role for the use of bicarbonate based continuous renal replacement therapies, such as continuous veno-venous hemodialysis (CVVHD) and hemofiltration.

Ketoacidosis

Ketoacidosis is caused by overproduction of ketoacids, primarily in the liver, as a result of an increase in the glucagon-to-insulin ratio. It occurs as a result of increase in fatty acid oxidation to ketone bodies. The two forms of ketoacidosis discussed further are diabetic and alcoholic ketoacidosis.

Diabetic Ketoacidosis (DKA)

DKA usually develops in association with an intercurrent illness (e.g., infection) that increases insulin requirement, increased fatty acid metabolism and causes accumulation of acetoacetate and β-hydroxybutyrate. Clinically, patients will present with nausea, vomiting, polydipsia, polyuria, and weakness. Volume depletion results from osmotic diuresis from hyperglycemia and fluid losses from vomiting.

Immediate therapy is aimed at inhibition of ketoacid production by administering insulin. Also, intravenous fluids need to be administered and electrolyte abnormalities corrected. It is not the purpose of this chapter to provide a guide for fluid/electrolyte administration in DKA. Note, however, that total body potassium is always depleted because of increased urinary losses induced by ketonuria, osmotic diuresis, high aldosterone levels, and vomiting. At presentation, potassium is typically paradoxically elevated (insulin deficiency results in shifting of the intracellular potassium into the extracellular space), but can decline fast with insulin administration; frequent potassium monitoring is mandatory. Phosphate levels may follow a similar course; frequent monitoring of serum phosphorus is again mandatory. Bicarbonate administration is generally avoided since there is a risk of developing an overshoot alkalosis from conversion of ketones to bicarbonate after insulin administration. Recently the use of bicarbonate in children presenting with DKA was shown to be associated with increase risk of developing cerebral edema. No direct causalit has been proven though.

Alcoholic Ketoacidosis

Occurs in chronic alcoholics and it is due to starvatio usually after binge drinking, followed by withdrawal. I is more common in women who are binge drinkers. Th predominant keto acid is β-hydroxybutyric acid, whic does not react with the reagent in the usual ketone tes kits; thus patients with alcoholic ketoacidosis may hav a false-negative ketone test. The acid-base picture i rarely a "pure" one. In addition to metabolic acidosi one can often find a metabolic alkalosis (from vomiting Estimating a delta anion gap/delta bicarbonate (Δ/Δ would help to characterize the acid-base disorder(s) i this case.

Therapy is aimed at intravenous fluid repletio and glucose administration. Glucose is importan because it increases the insulin-to-glucagon ratio which then suppresses the production of ketoacids Patients treated in this way are, however, at increase risk of developing "refeeding syndrome". Administratio of carbohydrates increases insulin release, an significant hypophosphatemia, hypokalemia an hypomagnesemia may occur. It is important to remembe this risk and evaluate carefully for development of sever hypophosphatemia, which can result in rhabdomyolysi hemolysis, platelet dysfunction, and respiratory failur Electrolyte replacement (potassium, phosphoru magnesium) is almost invariably needed.

Toxin-induced Acidosis

Plasma osmolality is "generated" mostly by sodiu glucose, and urea. Based on the molecular weight glucose and urea, plasma osmolality is calculated b following formula-

$$P_{osm} = 2Na^+ + Gluc/18 + BUN/2.8$$

$$\text{Alternatively, } P_{osm} = 2 \times Na + 10$$

There is generally a difference between calculate and actually measured osmolality, normally not great than 10 mOsm/kg. If this difference is higher, then w refer to it as osmolal gap. The osmolal gap is a result either pseudohyponatremia (seen in hyperlipidemi hyperproteinemia), or accumulation of osmolyt other than sodium, glucose, or urea. Examples such osmolytes are mannitol, radiocontrast agents, alcohols, ethylene glycol and acetone. The osmolal gap is proportional to the actual concentration of the unmeasured solutes. It then becomes a very important screening measure for toxin-induced high anion gap metabolic acidosis.

Salicylate Intoxication

There are many salicylate-containing over-the-counter products. The most commonly used however, is acetylsalicylic acid (aspirin -ASA). After ingestion it is rapidly converted to salicylic acid that is responsible for its toxic effects. Aspirin toxicity (acute or chronic) causes acid-base disturbances. Typically, there is a combination of metabolic acidosis (by causing uncoupling of the oxidative phosphorylation in the mitochondria, ASA leads to overproduction of lactic acid and ketoacids) and respiratory alkalosis (ASA stimulates the respiratory center). Salicylic acid itself does not contribute much to the increased anion gap. Tinnitus, vertigo, and gastrointestinal symptoms (nausea, vomiting, diarrhea) characterize early toxicity. More advanced stages are accompanied by coma with cerebral edema, a major cause of death in ASA intoxication. Therefore acute ASA intoxication should be treated as a real medical emergency that it is.

Gastric lavage should be performed and activated charcoal should be administered as soon as possible. An intravenous bicarbonate infusion should be started to alkalinize the blood and urine. In blood, the alkaline pH will reduce the diffusion of the nonionized fraction into the brain, whereas urine alkalinization will facilitate salicylate excretion. If renal failure is present, the rapid clearance of salicylate may be impaired. Hemodialysis is then indicated, as well as in patients who have neurologic findings, such as disorientation, stupor, or coma. Hemodialysis is also indicated when the serum salicylate level is greater than 100 mg/dL.

Ethylene Glycol Intoxication

The metabolic acidosis in ethylene glycol intoxication is due mostly to its major metabolite, glycolic acid. Lactic acid production is increased as well due to altered intracellular redox state. The final metabolite is oxalic acid that is responsible for the serious tissue damage to brain, heart, lungs and kidneys. Initially, patients appear intoxicated and can very rapidly develop seizures or coma. Later, cardiopulmonary dysfunction (heart failure, pulmonary edema) may develop. A constellation of high anion gap metabolic acidosis, high osmolal gap and oxalate crystals in the urine and acute kidney injury aid in the diagnosis.

Treatment of ethylene glycol intoxication is a medical emergency. It should be initiated promptly and consists of gastric lavage, saline or osmotic diuresis and thiamine and pyridoxine supplements. The alcohol dehydrogenase inhibitor 4-methylpyrazole (Fomepizole) has been used to inhibit (via a competitive mechanism) metabolism of ethylene glycol to its toxic metabolites and is shown to lessen the toxicity. It has the advantage of a predictable decline in ethylene glycol levels and evidently does not cause the obtundation seen with ethanol infusion. Alternatively, intravenous infusion of ethanol can be used to maintain a serum level of > 100 mg/dL to inhibit metabolism of the toxin. Treatment should also include hemodialysis early to remove ethylene glycol and its metabolites. Target serum level of ethylene glycol is <10 mg/dl. Ethanol levels should be monitored hourly and infusion rate has to be increased during dialysis to maintain the serum levels.

Methanol Intoxication

The acid responsible for the metabolic acidosis in methanol intoxication is formic acid. It causes severe central nervous system and optic nerve injury and can potentially result in irreversible blindness. Most patients have a history of alcoholism and ingest methanol accidentally. The best predictor of survival is the severity of acidosis. The molecular weight of methanol is low, thus the osmolal gap is usually quite high.

The treatment is generally the same as for ethylene glycol intoxication. Early initiation of hemodialysis to correct the acidosis and remove methanol and formic acid, as well as infusion of ethanol or fomepizole, is the key to effective therapy.

D-Lactic Acidosis

Bacterial overgrowth in the gastrointestinal tract (seen in jejunoileal bypass, short-bowel syndrome, ileus, intestinal obstruction, postantibiotic therapy) may result in production and absorption of D-lactate. This results in an increased anion gap metabolic acidosis with neurological symptoms (especially ataxia). The routine measurement of serum lactate identifies L-lactate but not the D-lactate; thus once suspected, D-lactate has to be specifically ordered. It is the accumulation of toxic products and not the acidosis that poses a potential danger to the patients' life in D-lactic acidosis.

The treatment is aimed at the eradication of bacterial overgrowth. Attempts should be made to increase the gastrointestinal motility and feeding should be temporarily stopped. Long-term antibiotic therapy (such as metronidazole) may be indicated. Removal of the jejunoileal bypass, or correction of anatomical defect may be required if stasis/ bacterial overgrowth are recurrent.

Non Anion Gap (Hyperchloremic) Metabolic Acidosis

A normal AG on a routine electrolyte panel, with a lower HCO_3^- and hyperchloremia suggests either a metabolic acidosis or a respiratory alkalosis (or a combination of both). The only way to diagnose the acid-base abnormality present is by performing an arterial blood gas (ABG). Four groups of disorders can cause this state (Table 1): gastrointestinal (GI) losses of HCO_3^-, renal losses of HCO_3^-, ureteral diversion procedures, and inorganic acid intake.

Gastrointestinal HCO_3^- Loss

The GI tract distal to the stomach functions like a Cl^- absorbing, HCO_3^- secreting organ. Diarrhea, pancreatic and biliary fistulae will then cause external loss of HCO_3^- rich fluids. Fluid that is relatively Cl^- rich is retained, generating a hyperchloremic metabolic acidosis, with normal anion gap. Similarly, when normal urine (rich in sodium chloride from dietary sources) is drained into the gut via ureterosigmoidostomy or ileal loop conduit, Cl^- can be reabsorbed in exchange for HCO_3^- resulting in hyperchloremic metabolic acidosis. This is especially likely to occur if there is obstruction to the urine flow resulting in stagnation of urine.

The treatment consists of correction of stomal stenosis and bicarbonate replacement.

Table 1. Causes of hyperchloremic metabolic acidosis

1. Increase in HCl (NH_4Cl, TPN, lysine, arginine).
2. Gastrointestinal loss of bicarbonate.
3. Uretero-gastrointestinal diversion and fistula.
4. Posthypocapnic acidosis.
5. Early stage or post therapy of diabetic ketoacidosis (loss of ketoacids in the urine).
6. Renal tubular acidosis.

Inorganic Acid Intake

This is a much more rarely seen condition. hyperchloremic metabolic acidosis may be produce by ingestion of NH_4Cl (taken to suppress appetite, o acidify the urine) and of sulfur (used in the past, flower of sulfur cathartic).

Renal Tubular Acidosis (RTA)

RTA (Table 2) is the result of defective H^+ secretion a the proximal tubule level, distal nephron, or both sites Metabolic acidosis of renal cause in the setting of rena insufficiency is usually an elevated anion gap acidosis Typically, it occurs when GFR is ≤ 30 mL/min. In th case of RTA, the degree of metabolic acidosis is ou of proportion (as compared to the one seen in rena insufficiency) to the GFR level. Replacement of HCO_3^- los from plasma with Cl^- results in hyperchloremia.

Proximal RTA (Type II)

It is usually associated with generalized transporte dysfunction of the proximal tubule (Fanconi's syndrome) The pathophysiology of this type of RTA is reduced abilit of the proximal tubule to reclaim filtered HCO_3^- . Thi results in HCO_3^- wasting. Renal loss of other substance occurs as well (e.g., glucose, amino acids, phosphate uric acid). The proximal tubule capacity for HCO reabsorption is decreased, but not totally absent. Thus once the serum bicarbonate decreases to a certai "threshold", the HCO_3^- wasting ceases and the urin becomes HCO_3^- free, with an acidic pH. Thus proxim RTA is a self-limited disorder. Patients with proximal RT will generally present when they are already in a ne "steady state". Therefore, they will have a urine pH of les than 5.5. Supplementing them with HCO_3^- will "resume the wasting process and urine pH will increase to > 6. Because of this "self-limited" wasting, the serum HCO is generally not lower than 14 to 20 mEq/L. To aid in th diagnosis, we can measure the fractional excretion HCO_3^-. It is generally greater than 10 to 15 percent, at near-normal serum HCO_3^- level.

Table 2. RTA classification

- Proximal (Type 2)
- Distal (Type 1)
- Hyperkalemic Distal RTA (Type 4)

Proximal RTA is seen in adults in association with multiple myeloma, chronic interstitial nephritis, transplant rejection and ingestion of agents toxic to the renal tubules or use of carbonic anhydrase inhibitors. The treatment is aimed at replacing the HCO_3^- loss. However serum HCO_3^- level cannot be restored to normal usually, due to the continuous urinary "leak" of HCO_3^-. Caution should be used when administering large doses of oral or intravenous HCO_3^- replacement, as this may result in very severe (even fatal) hypokalemia by increasing distal K^+ secretion. Administration of $KHCO_3$ is therefore preferred.

Distal RTA

Distal RTA differs from the proximal form, in that it is caused by a defect of the collecting ducts in which a small HCO_3^- leak occurs daily, thus the endogenous acid production cannot be excreted totally. There are two types of distal RTA:

Type I distal RTA may be hereditary (usually manifested in childhood) or sporadic (seen in association with autoimmune syndromes, amyloidosis, medullary sponge kidney, cirrhosis of the liver, transplant rejection, certain drugs such as amphotericin B and foscarnet). It is caused by defective H^+ secretion in the collecting ducts. The collecting duct K^+ secretion is intact and actually enhanced by the bicarbonaturia. The result is hypokalemia, which accompanies this form of RTA. The HCO_3^- wastage is small but continuous; thus the serum HCO_3^- levels can fall to extremely low levels (< 10 mEq/L).

The hyperkalemic variant of type I RTA results from diminished distal tubular Na reabsorption, which reduces the negative intraluminal gradient and, as a result, decreases both H and K secretion. It may occur in urinary tract obstruction, lupus nephritis, sickle cell disease and volume depletion with decreased distal sodium delivery. The hyperkalemic variant of type I RTA is differentiated from type 4 RTA by having a urine pH above 5.5, a serum bicarbonate usually less than 15 meq/L and normal aldosterone level. In comparison, patients with type 4 RTA, usually have serum bicarbonate above 17 meq/L and urine pH of less than 5.3.

Patients with type I distal RTA cannot acidify their urine to a pH < 5.5, even after an oral load of NH_4Cl. They also have a reduced excretion of urinary citrate (also due to the more severe metabolic acidosis), which predisposes them to nephrolithiasis and nephrocalcinosis. Typically, they tend to form calcium phosphate (brushite) stones. Treatment is aimed at correcting the serum K^+ first, then the metabolic acidosis. Otherwise, development of alkalemia can worsen the hypokalemia to very dangerous levels. In most patients, eventually HCO_3^- replacement alone is sufficient to correct both the acidosis and hypokalemia. After normalizing first the serum HCO_3^-, daily supplementation approximately equal to the endogenous acid production (50 to 75 mEq/day) is usually enough. Correction of the metabolic acidosis also controls the nephrocalcinosis in most patients. In some patients hypokalemia is very severe requiring large dose of potassium replacement therapy. Urine potassium is high and aldosterone level can be high.

Type 4 RTA is the more common form of RTA seen in medical practice. It occurs when collecting duct K^+ secretion is impaired by either a tubular defect itself, or hypoaldosteronism, which may be secondary to aldosterone deficiency or resistance to its actions. The most common cause of type IV distal RTA is diabetic nephropathy, usually associated with hyporeninemic hypoaldosteronism. Aldosterone deficiency results from adrenal insufficiency, congenital adrenal hyperplasia, high and low molecular weight heparin, isolated aldosterone synthase deficiency, while hyporeninemic hypoaldosteronism results from drugs (ACEI, CSA, NSAIDS), diabetic nephropathy, volume expansion, HIV, and urinary obstruction. Aldosterone resistance may result from drugs like triamterene, amiloride, aldosterone receptor antagonists (spironolactone and eplerenone), trimethoprim, and pentamidine, as well as tubulointerstitial nephritis, distal chloride shunt and pseudohypoaldosteronism.

The metabolic acidosis is generally mild (serum HCO_3^- of 16 to 20 mEq/L). Mechanisms that are involved in the impaired acidification include suppression of NH_4^+ production/excretion by hyperkalemia, impaired distal tubular H^+ secretion, and hypoaldosteronism. Treatment of type IV distal RTA is aimed at reducing the serum K^+ level and increasing the HCO_3^- level. As mentioned above, hyperkalemia decreases NH_4^+ production. Correcting it will result in increased NH_4^+ production and correction of the serum HCO_3^-. It is therefore the key part in the treatment of this form of RTA. Dietary modifications may be sufficient, but occasionally chronic use of Kayexalate (sodium polystyrene sulfonate) is needed. An adjunctive measure is evidently HCO_3^- administration, which alkalinizes the blood; this ultimately results in increased distal potassium excretion. Sometimes, administration of mineralocorticoid replacement (in patients with hypoaldosteronism) such as fludrocortisone 0.1 to 0.5 mg, orally per day is essential. Close monitoring of such patients is recommended to avoid development of volume expansion and worsening of hypertension.

METABOLIC ALKALOSIS

Metabolic alkalosis is a common clinical disorder, which results from an increase in plasma bicarbonate. Its pathogenesis involves both the generation of metabolic alkalosis and the maintenance of metabolic alkalosis. The generation of bicarbonate results from the loss of hydrogen ions and/or the addition of new bicarbonate. Impaired renal capacity to secrete excess bicarbonate or enhanced kidneys reclamation of bicarbonate are important factors to maintain metabolic alkalosis.

Causes of Metabolic Alkalosis

1. Gastrointestinal losses as in vomiting, nasogastric suctioning, and loss of intestinal secretions, which may occur in villous adenoma and laxative abuse with factitious diarrhea.
2. Renal losses result from the combined effect of increased distal sodium delivery to the distal nephron and increased mineralocorticoid activity because of volume contraction, This, in turn, leads to enhanced sodium reabsorption by the sodium channels in the principle cells and creation of more electronegative charge in the lumen of the collecting duct, which facilitates the secretion of both hydrogen ions and potassium into the lumen. This is the mechanism of metabolic alkalosis with the use of loop and thiazide diuretics and in both Bartter's (lasix without Lasix) and Gitelman's (Thiazide without thiazide) syndromes.
3. Primary mineralocorticoid hyperactivity as in primary hyperaldosteronism: The primary increase in mineralocorticoids leads to both increased sodium reabsorption in the sodium channels and increased distal sodium delivery to the distal tubules because of volume expansion. A similar mechanism is present in Liddle syndrome, which results from a gain of function of the sodium channel in the collecting duct.
4. Intracellular shifts of hydrogen ions: This usually occurs in patients with hypokalemia. In this condition, as potassium moves out of the cells to replete the extracellular stores, hydrogen ions move into the cells to maintain electroneutrality.
5. Posthypercapnic alkalosis: The compensatory response in respiratory acidosis is the increase in plasma bicarbonate to mitigate the decrease in blood pH. Rapid correction of chronic respiratory acidosis as in mechanical ventilation leads to the development of metabolic alkalosis.
6. Alkali administration: Administration of alkali that exceeds the ability of the kidneys to excrete excess bicarbonate leads to the development of metabolic alkalosis. The excess of both bicarbonate and bicarbonate equivalents like lactate, acetate, and B-hydroxybutyrate (which are metabolized to bicarbonate) may lead to the development of metabolic alkalosis.
7. Contraction alkalosis: The loss of large volume of bicarbonate-poor fluid leads to volume depletion. The plasma bicarbonate concentration increases as the relatively unchanged extracellular bicarbonate is present in a less fluid volume.
8. Milk alkali syndrome and hypercalcemia: Metabolic alkalosis results from the increase in alkaline load and hypercalcemia, which leads to increased bicarbonate reabsorption by the kidneys.
9. Congenital chloridorrhea: Metabolic alkalosis results from the increased secretion of chloride with the diarrhea and reabsorption of bicarbonate.

To simplify differential diagnosis of metabolic alkalosis, its causes can be divided into chloride responsive and chloride resistant metabolic acidosis.

Chloride-responsive (urine chloride is 20 meq/L)

A. Loss of hydrogen ions
   1. Gastrointestinal loss- vomiting, nasogastric suctioning, villous adenoma, and congenital chloridorrhea.
   2. Renal loss- post diuretics effect
B. Post hypercapnic alkalosis
C. Contraction alkalosis.
D. Cystic fibrosis

Chloride-resistant (urine chloride is more than 20 meq/L)

A. Primary mineralocorticoid overactivity
   1. Primary hyperaldosteronism
   2. Congenital adrenal hyperplasia

    3. Apparent mineralocorticoid activity (Licorice and carbenoxolone)
    4. Cushing syndrome and glucocorticoids/mineralocorticoids ingestion

B. Ongoing use of loop and thiazide diuretics
C. Bartter's and Gitelman's syndromes (low BP)
D. Liddle syndrome (activation of sodium channel, ENaC)
E. Renal vascular hypertension
F. Potassium depletion
G. Alkalotic agents in excess and milk alkali syndrome.
H. Hypomagnesemia
I. Hypercalcemia
J. Increased delivery of unabsorbable anions to the distal nephron (nafcillin and penicillin)

Treatment

Treatment of metabolic alkalosis includes correction of the etiologic factor and varies according to its type. In chloride responsive metabolic alkalosis, correction of volume depletion with normal saline results in bicarbonate excretion by the kidneys. In patients with chloride responsive metabolic alkalosis and volume overload as in cirrhosis and congestive heart failure the use of acetazolamide, which inhibits proximal tubular bicarbonate reabsorption is recommended. In either case, correction of the underlying electrolyte abnormalities like hypokalemia and hypomagnesemia is of paramount importance in management of metabolic alkalosis.

In chloride resistant metabolic alkalosis correcting or mitigating of the underlying etiology is the major factor in management. In patients with primary hyperaldosteronism, surgical removal of adrenal adenoma and the use of aldosterone receptor blockers (spironolactone and eplerenone) and potassium sparing agents (amiloride and triamterene) improves hypokalemia and metabolic alkalosis. In patients with Liddle syndrome, the use of potassium sparing agents but not aldosterone receptor blockers corrects metabolic alkalosis. In glucocorticoid remediable hyperaldosteronism, the use of dexamethasone suppresses both cortisol and aldosterone production and improves the alkalosis.

The use of isotonic hydrochloric acid, which buffers excess bicarbonate is effective in patients with severe metabolic alkalosis, not responsive to other therapies and when rapid correction is necessary.

Clinical Approach to Acid Base Disorders

Evaluation of acid-base disorder should start with blood pH to determine the primary disorder. It is important to remember that acidemia and alkalemia refer to changes in the blood pH, while acidosis and alkalosis refer to processes that tend to lower or raise the pH. For instance, in a patient with acidemia, more than one process may be present. Primary changes in pCO_2 are called respiratory acidosis, when the pCO_2 is elevated and respiratory alkalosis, when the pCO_2 is decreased. A pH of less than 7.36 is called acidemia, which suggests a primary metabolic acidosis if the bicarbonate is low and a primary respiratory acidosis if the pCO_2 is high. A pH of more than 7.44 is called alkalemia, where elevated bicarbonate suggests a primary metabolic alkalosis and low pCO_2 suggests a primary respiratory alkalosis. The next step is to determine the compensatory response. Here it is important to remember that the compensatory response always goes in the same direction as the primary abnormality and a normal pH in the presence of acid-base disorder is usually secondary to a mixed disorder. Table 3 shows normal compensation in acid-base disorders.

Next knowing the anion gap is very important to differentiate between gap and non gap acidosis. The calculation of the delta/delta ratio ($\Delta AG/\Delta HCO_3^-$), which is the ratio between the change in the anion gap and the change in the plasma bicarbonate concentration is very useful subsequent (to AG) calculation (Table 4). In an uncomplicated anion gap metabolic acidosis $\Delta AG/\Delta HCO_3$ is usually 1 to 2. Δ AG/Δ HCO_3 of less than 1 is suggestive of the presence of a concurrent nonanion gap metabolic acidosis, while a Δ AG/Δ HCO_3 of more than 2 is suggestive of the presence of metabolic alkalosis.

Clinical Cases

Case 1. A 30-year-old female presents to the emergency room with mental status changes and with smell of alcohol in her breath. Laboratory evaluation shows Na of 138, K 3.8, Cl 104, CO_2 13, creatinine 0.9. Arterial blood gases show pH of 7.34, pCO_2 28, pO_2 99. What acid-base abnormality is present?

Clinical approach

Table 3. Normal compensation in acid-base disorders

- Metabolic Acidosis (↓ HCO_3)
  - 1.2 ↓ in PCO_2 for 1 mEq/dL ↓ in HCO_3 or
  - $pCO_2 = 1.5 \times [HCO_3^-] + 8\ (\pm)2$
- Metabolic Alkalosis (↑ HCO_3)
  - 0.7 ↑ in PCO_2 for every 1 mEq/dL ↑ in HCO_3
- Respiratory Acidosis (↑ pCO_2)
  - ACUTE HCO_3 ↑ by 1 per 10 Δ pCO_2
  - CHRONIC HCO_3 ↑ by 3.5 per 10 Δ pCO_2
- Respiratory Alkalosis (↓ CO_2)
  - ACUTE HCO_3 ↓ by 2 per 10 Δ pCO_2
  - CHRONIC HCO_3 ↓ by 4 per 10 Δ pCO_2

Table 4. Types of metabolic acidosis

	Na	*K*	*Cl*	*HCO_3*	*AG*	Δ *AG*	Δ *HCO_3*	Δ *AG/* Δ *HCO_3*
Normal	138	4	104	24	10	0	0	0
Pure high anion gap	138	4	104	14	20	10	10	1.0
Pure HCA	138	4	114	14	10	0	10	0
Mixed	138	4	110	12	16	6	12	<1

HCA = Hyperchloremic acidosis

- pH is low → acidemia
- Anion gap: 138 - (104 + 13) = 21
- Expected PCO_2: 26 to 30

The answer is compensated anion gap acidosis

Case 2. A 25-year-old female presents with peri-oral paresthesias and dental erosions. Her laboratory evaluation shows Na 140, K 5.0, Cl 91, HCO_3^- 40; arterial blood gas analysis shows pH 7.50, pCO_2 51. Urine chloride was 8 mEq/L. What acid-base abnormality is present?

Clinical approach

1. Primary acid-base disturbance?
   pH > 7.5 → alkalemia
   ↑ HCO_3^-/ ↑ pCO_2? → answer: ↑ HCO_3^- → metabolic alkalosis
2. Anion Gap? 140 - (91 + 40) = 9
3. Compensation?
   Expected $pCO_2 = 0.7 \times 16 = 11\ (40+11=51)$ → compensated metabolic alkalosis.
4. Differential diagnosis: Cl- responsive vs. Cl- resistant metabolic alkalosis → chloride responsive metabolic alkalosis.
5. Oral examination? ... suggestive of bulimia

Answer: Compensated metabolic alkalosis secondary to recurrent vomiting.

Case 3. 60-year-old male with hypertension, diabetes and coronary artery disease, develops dyspnea and profound weakness with cyanosis. Laboratory evaluation shows Na 134, K 4.4, Cl 80, HCO_3 20; glucose 245 and blood gas analysis showed pH 7.20, pCO_2 52, pO_2 40. What acid-base abnormality is present?

- Primary acid-base disturbance: pH < 7.36 (acidemia)
- ↓ HCO_3^- and ↑ pCO_2 answer: both metabolic and respiratory acidosis
- Anion gap = 134 - (80 + 20) = 34; Δ AG/Δ Bicarb = 24/4 = > 2 ---- Metabolic alkalosis (The delta anion gap is 24, which is the absence of a source of alkali will lead to serum bicarbonate of 0, as each mEq of acid will destroy one mEq of alkali; please refer to clinical approach to acid-base disorders).
- Diagnosis: Respiratory acidosis, AG metabolic acidosis and metabolic alkalosis

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8

Metabolic Alkalosis: Pathophysiology and Management

Anil K Mandal

INTRODUCTION

Metabolic alkalosis (metabolic alkalemia) might have the most common acid-base disorder among the hospitalized patients in the past. Metabolic alkalosis is frequently accompanied by severe hypokalemia and less often cardiac arrhythmias which warrant hospital admission. In arterial blood gas analysis from Loma Linda University, California, simple metabolic alkalosis was found in 36 percent of patients with abnormal acid-base status. Metabolic alkalosis can be simple; it is often associated with chronic respiratory acidosis or mixed with respiratory alkalosis. Although simple metabolic alkalosis may be more common than other acid-base disorders in large metropolitan or university hospitals population, mixed respiratory acidosis and metabolic alkalosis is apparently more common in the veterans hospitals and community hospitals population. This mixed disorder is most frequently induced by excessive diuretic therapy. The diuretics enhance HCO_3^- reabsorption throughout the nephron and markedly increases serum HCO_3^- level. Blood pH reaches normal level or becomes overtly alkalemic.

In the outpatient setting or in office practice, diuretic therapy is the most common cause of metabolic alkalosis. It is generally a laboratory finding as the patient is asymptomatic. However, severe metabolic alkalosis as seen in surgical floor of a hospital generally makes patient symptomatic such as tetany or convulsion warranting intensive therapy.

DEVELOPMENT OF METABOLIC ALKALOSIS

The development (or generation as commonly stated) of metabolic alkalosis is initiated by extrarenal or renal mechanisms. These are presented in Table 1. Persistent vomiting or gastric suction causes loss of hydrogen and chloride ions as well as volume, thereby, elevating serum HCO_3^- level and reducing serum chloride level. Volume depletion enhances HCO_3^- reabsorption by the kidneys (will be discussed later).

Table 1. Development (Generation) of metabolic alkalosis

Extrarenal Mechanisms	*Renal Mechanisms*
Persistent vomiting (pyloric stenosis, gastritis)	Diuretic therapy
Nasogastic suction (postsurgery, ileus)	Primary or secondary hyperaldosteronism
Excessive intake of bicarbonate or citrate/acetate mixture for metabolic acidosis	Corticosteroid therapy
Milk-bicarbonate (Milk-Alkali Syndrome)	Poorly absorbable/nonabsorbable anions, including carbenicillin, penicillin
Congenital chloride diarrhea	Hypercalcemia not associated with hyperparathyroidism
Overshoot alkalosis (e.g., Ketoacidosis, Lactic acidosis)	Surreptitious vomiting

Diuretic, aldosterone or cortisol stimulates H^+ and K^+ loss from tubule cells resulting in excessive bicarbonate reabsorption and hypokalemia.

The development of hyperbicarbonatemia is not very critical, since bicarbonate is rapidly excreted by kidneys. Therefore maintenance of metabolic alkalosis is more critical than its development.

Mechanism of Maintenance of Metabolic Alkalosis

Maintenance of metabolic alkalosis is essentially a function of the kidneys. In this context, it is important to have some understanding of bicarbonate handling by the kidneys. Like Na^+ and other small solutes, HCO_3^- is freely filtered by the glomeruli. Hydrogen ion is secreted into the tubular lumen throughout the nephron. H^+ combines with filtered HCO_3^- to form H_2CO_3, which within milliseconds dissociates into CO_2, which then diffuses into the cell and peritubular fluid. The OH^-, which is formed from the dissociation of H_2O, combines with CO_2 again under the influence of carbonic anhydrase to form HCO_3^-, which diffuses into the peritubular blood. Since carbonic anhydrase is mostly present in proximal tubule, HCO_3^- reabsorption is greatest in the proximal tubule.

The hydrogen ion secretion by the renal tubules operates in such a manner that when the plasma bicarbonate is below a threshold level, reabsorption of bicarbonate is complete, and no bicarbonate appears in the urine. However, as the plasma bicarbonate concentration is increased above this threshold level, reabsorption does not increase proportionately and excretion of bicarbonate into the urine begins. The maximal rate of bicarbonate reabsorption varies among different species and is approximately 28 mEq/L GFR in man, 25 mEq/L GFR in dogs and 35 mEq/L GFR in rats. Further increases in plasma HCO_3^- concentration produce only slight changes in reabsorption and the system exhibits an apparent transport maximum. There is, however, no true transport maximum TM for bicarbonate reabsorption (via hydrogen ion secretion).

There are permissive effects of extracellular fluid (ECF) volume, PCO_2, and plasma chloride concentration on HCO_3^- reabsorption. When ECF volume is expanded markedly, as by the infusion of NaCl or $NaHCO_3^-$ reabsorption of filtered HCO_3 is decreased, and the reverse holds true when ECF volume is contracted. It should be noted that when plasma HCO_3^- level is raised without ECF volume expansion by means o dialysis against a low Cl or high HCO_3^- or when volume is contracted by controlled hemorrhage or partial vena caval obstruction, then plasma HCO_3^- progressively increases. HCO_3^- reabsorption is directly related to PCO_2 As PCO_2 is increased, the HCO_3^- reabsorption is enhanced and vice versa. The effect is more marked during chronic than acute alteration of PCO_2. The mechanism by which PCO_2 affects HCO_3^- reabsorption is not completely clear It is felt that this is due to extent of supply of CO_2 substrate to tubule cell, but there may be other mechanism(s involved. Finally, there is a well-known reciproca relationship between plasma concentration of Cl^- and that of HCO_3^-. In most situations, as the plasma Cl concentration falls, that of HCO_3^- rises and vice versa. This reciprocal relationships involves the critical importance of maintaining ECF volume, and hence Na^+ balance; tha is Na^+ reabsorption must be maintained, and in order to preserve electroneutrality, either Cl^- or HCO_3^- mus accompany reabsorbed Na^+. In any case, as chloride concentration rises, that of HCO_3^- falls.

Factors influencing proximal and distal HCO_3 reabsorption are shown in Tables 2, 3, and 4. Factors influencing maintenance of metabolic alkalosis are presented in Table 5.

ECF volume contraction leads to decrease in GFR which occurs in most or all patients with metabolic alkalosis. Although the plasma concentration of HCO_3^- is elevated, the kidney perceives less of filtered bicarbonate Thus, proximal tubular bicarbonate reabsorption is enhanced. In addition, ECF volume contraction may have an effect, independent of filtered load, to enhance proximal bicarbonate reabsorption.

Hypochloremia, independent of volume contraction stimulates renin release resulting in a decrease in GFR As before, this decrement in GFR decreases filtered load of HCO_3^- and decreases HCO_3^- excretion.

Hypokalemia and mineralocorticoid excess, such as primary and secondary hyperaldosteronism, Cushing syndrome, Bartter's syndrome, Liddle syndrome, al maintain metabolic alkalosis, through a common pathway. Hypokalemia decreases GFR by increasing renal vascular resistance and through decreased GFR enhances proximal HCO_3^- reabsorption. Hypokalemia also enhances distal HCO_3^- reabsorption. The passive bicarbonate back flux many have an effect in metabolic alkalosis. The increase in salt and water reabsorption

Table 2. Factors influencing the rate at which filtered HCO_3^- is reabsorbed

1. Amount of HCO_3^- presented to the tubules
2. State of ECF volume
3. Arterial PCO_2
4. Plasma Cl^- concentration
5. Certain hormones.

Table 3. Factors influencing proximal HCO_3^- absorption

- ECF volume contraction
- Hypokalemia
- Hypercapnea
- PTH deficit (?)
- Hypercalcemia
- Hyperglycemia
- Acidemia

Table 4. Factors influencing distal HCO_3^- absorption

- Aldosterone excess
  - ↑ Sodium transport
  - ↑ Negativity of the lumen
- Hypokalemia
- Hypercapnea (?)
- Nonabsorbable anion (e.g., carbenicillin)

Table 5. Factors influencing maintenance of metabolic alkalosis

1. ECF volume contraction
2. Hypochloremia
3. Hypokalemia
4. Mineralocorticoid excess
5. Passive bicarbonate backflux
6. Renal failure treated with high dose of HCO_3^-
7. Post-hypercapneic state

Table 6. Urinary chloride concentration as a determinant of volume and mineralocorticoid status

Urine Chloride ≤ 20 mEq/L Chloride Responsive	*Urine Chloride >20 mEq/L Chloride Resistant*
Vomiting	Cushing syndrome
Nasogastric suction	Hyperaldosteronism
Diuretics	Paraneoplastic syndrome
Congenital chloride diarrhea	Severe potassium deficiency
Villous Adenoma of Colon	Bartter's syndrome
Posthypercapnea	Liddle's syndrome
Excessive HCO_3^- intake	Licorice ingestion
Blood transfusion	Refeeding (glucose) alkalosis
	Hypercalcemia/ hypoparathyroidism

in the proximal tubule is accompanied by increasing HCO_3^- concentration in the tubular lumen. This increased concentration in the tubular lumen may cause backflux of HCO_3^- into the blood and help maintain metabolic alkalosis.

In renal failure, the ability to excrete bicarbonate by the kidneys remains active. It has been observed that patients with advanced renal disease become edema-free, if NaCl in the diet is substituted by $NaHCO_3$. However, excessive bicarbonate loads in the presence of renal failure can produce alkalosis with or without edema.

If chronic hypercapnea is relieved by intubation or tracheostomy, elevated serum HCO_3^- is still maintained high. This appears to be due to ECF volume contraction and can be corrected by increasing dietary salt or by infusion of isotonic saline solution.

DIAGNOSIS

The most important diagnostic test of metabolic alkalosis is urinary chloride which will distinguish between chloride responsive (low urine Cl^-) and chloride resistant (high urine Cl^-) metabolic alkalosis.

The various chloride responsive and chloride resistant states are shown in Table 6. If no cause for metabolic alkalosis is evident, a thorough physical examination can be a helpful guide to identify the cause of metabolic alkalosis. Blood pressure is a good predictor. While normal blood pressure in the setting of hypokalemia and metabolic alkalosis signifies Bartter's syndrome, elevated blood pressure suggests primary or secondary hyperaldosteronism, Liddle syndrome or licorice ingestion.

MANAGEMENT

Management will depend upon

1. Urine chloride level
2. State of ECF volume.

It should be noted that serum K^+ is not a determining factor in the management of metabolic alkalosis. Thus, if urine chloride is equal to or less than 20 mEq/L and evidence of ECF fluid volume depletion is present (e.g., postural hypotension, tachycardia, oliguria, decreased renal function), administration of normal saline is the treatment of choice. Small amounts of KCl such as, 20 mEq should be added in each liter bag of normal saline. Rate of infusion will depend on symptoms, blood pressure and heart condition. Generally 75 to 100 ml per hour for 48 to 72 hours is adequate.

H_2 receptor blocker such as ranitidine, Pepcid® p.o. or IV is additive. Ranitidine 150 mg po twice daily or 150 mg IV once daily or Pepcid® 20 mg po twice daily or 20 mg IV once daily has been very effective in reducing H^+ and Cl^- loss and mitigating the severity of alkalosis. If the patient has persistent vomiting, or requires nasogastic suction, ranitidine (150 mg) can be given intravenously twice daily.

On the other hand, if urine Cl^- is high (>20 mEq/L) and serum K^+ is very low, treatment will consist of K^+ supplementation and/or a potassium sparing agent. 24-hour urine K^+ should be obtained. Potassium chloride can be given in a does of 20 to 30 mEq orally every 6 hours. In addition, if pH is higher than 7.55 and serum bicarbonate is above 40 mEq/L, acetazolamide (Diamox®) should be used to reduce promptly serum bicarbonate level and hence pH. See later for dosage of acetazolamide. If serum K^+ does not rise in 48 to 72 hours, serum magnesium should be measured and if found low, magnesium should be replaced in the form of magnesium sulfate IM or magnesium oxide po (for magnesium administration see chapter on hypokalemia). If urinary K^+ loss is very high (200 to 300 mEq/day), K^+ sparing agent can be added to the regimen. Three K^+ sparing agents are available:

1. Spironolactone
2. Triamterene
3. Amiloride

While spironolactone (Aldactone®) is preferable in cases with primary hyperaldosteronism, triamterene and amiloride can be used irrespective of aldosterone level. If Bartter's syndrome is the diagnosis, spironolactone is very effective. Spironolactone is also very effective in correcting hypokalemia in congestive heart failure and cirrhosis of liver. Other drugs that can be used in Bartter's syndrome include prostaglandin synthesis inhibitor, such as indomethacin 25 mg orally three times daily. Side effects of indomethacin include bleedi peptic ulcer, sodium retention and edema, elevation blood pressure, and rarely acute interstitial nephri with heavy proteinuria and renal failure. Another dr worth considering in Bartter's syndrome is angioten converting enzyme inhibitor (ACEI), such as captop 25 mg orally three times daily.

Spironolactone is a slow acting drug, where triamterene and amiloride are fast acting dru Beta blockers can be used instead of ACEI, to inhi translocation of K^+ into intracellular fluid.

DOSAGE REGIMEN AND SIDE EFFECTS

Spironolactone: 25 mg tablet, 25 mg Q 6h. Slo increase every three days. Max dose: 400 mg/day.

Side effects are common and include bilateral, pain breast and decreased libido in females; gynecomas and impotence in males, hyperkalemia.

Triamterene (Dyrenium®): 50 mg tablet, 50 mg twi daily. Max dose: 200 mg/day.

Side effects are uncommon, but include hyperkalem megaloblastic anemia and renal stones.

Amiloride (Midamor®): 5 mg tablet, 5 mg twice dai Max dose: 20 mg/day.

Side effects are uncommon, but include hyperchloren metabolic acidosis and hyperkalemia.

For more details about potassium sparing agents, s Chapter on Hypokalemia and Hyperkalemia.

Management of Metabolic Alkalosis with Volume Overload but Low Urinary Chloride

The following agents should be considered:

1. Acetazolamide (Diamox®)
2. Acidifying Agents
   a. NH_4Cl
   b. $CaCl_2$
   c. Arginine hydrochloride
   d. HCl

Diamox® can be given as 250 mg Q 6h orally or 250 500 mg Q 12h intravenously. Acetazolamide enhanc bicarbonate excretion.

Side effects of Diamox® include hypokalemia a hyperchloremic metabolic acidosis. NH_4Cl, CaC arginine hydrochloride are seldom used nowada In severe metabolic alkalosis and critically ill patien HCl can be used and administered as follows.

Administration of HCl

Route: Central vein
Solution: 0.1 to 0.2 M solution
Dosage: 15 to 20 mEq per hour

Total amount of HCl to be infused will depend on serum HCO_3. If serum HCO_3 is 50. Desirable HCO_3 is 30 mEq/L; 20 mEq/L decrease of bicarbonate is considered. ECF volume 14 liters x 20 = 289 mEq HCl.

Monitor: Arterial blood gas every four hours to control progress and continuity of administration.

Metabolic Alkalosis with Volume Overload

Moderate to severe renal failure (serum creatinine ≥ 3.5 mg/dL).

TREATMENT OF CHOICE

Hemodialysis Using

A. Low-bicarbonate dialysate or
B. High-chloride and low-acetate dialysate

Specific Indications

1. Cardiac Arrhythmias
2. Seizures
3. Tetany
4. Respiratory Distress

Acetazolamide can also be tried in short of hemodialysis.

KEY POINTS

1. Metabolic alkalosis is a common disorder in an outpatient setting. It is often mild and asymptomatic.
2. Prompt recognition and effective treatment of severe metabolic alkalosis is essential.
3. Delay in the initiation of treatment could result in high morbidity and mortality.
4. Mortality increases in parallel with arterial blood pH. In one series, it was 45 percent with arterial pH of 7.55 and 80 percent when pH exceeded 7.65.

Causes of Morbidity and Mortality are as follows:

1. Hypocalcemia as a result of—
    a. Alkalemia decreases release of Ca^{++} from bone.
    b. Alkalemia enhances albumin binding of Ca^{++}.
2. Severe hypokalemia
3. #1 and #2 lead to increased propensity to cardiac arrhythmias and digitalis toxicity
4. Enhanced glycolysis and tendency to hypoglycemia
5. Hypocalcemia and hypoglycemia lead to grand mal convulsions
6. Compensatory hypoventilation
    → Atelectasis: Hypoxia-infection
7. Shifting of O_2 dissociation curve to the left interfering with O_2 release to tissue.

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9

Polyuria and Diabetes Insipidus

Anil K Man

POLYURIA

Background

Polyuria is the excretion of an excessive volume of urine per unit time; it is associated with increased frequency of urination to accommodate the large volume of urine produced. Polyuria is not to be confused with the frequency of urination caused by genitourinary tract infections such as urethritis, cystitis, and prostatism. This is accompanied by dysuria, a small volume of concentrated urine, and sometimes abnormal-appearing urine; the urinalysis is almost always abnormal. In contrast, polyuria caused by diabetes insipidus, diabetes mellitus, chronic renal disease, or compulsive water drinking is accompanied by polydipsia, elimination of very dilute urine, sleeplessness, and tiredness; generally the urinalysis is normal. A thorough patient history, complete physical examination, and laboratory testing should establish the cause of polyuria in a given patient and help in formulating an appropriate plan for management.

Causes

The major causes of polyuria are listed in Table 1. The causes can be determined provided the mechanism of urinary concentration is well understood. Urinary concentration is determined by:

- Urinary flow rate
- Urinary solute load
- Medullary interstitial osmolality
- Plasma vasopressin level
- State of collecting tubule responsiveness to arginine vasopressin (AVP) or antidiuretic hormone (ADH)

Urinary Flow Rate

Pathophysiologically, expanded extracellular flu volume increases the glomerular filtration rate (GFI which increases urinary volume and frequenc Expansion of the extracellular fluid volume can occ as a result of excessive intake of free water or other typ of fluids. Typical examples of excessive fluid intal include that by compulsive water drinkers and hea beer drinkers.

Excessive Solute Load

An excessive solute load, such as glucose, sodiu chloride, and urea, can give rise to polyuria and increase urinary frequency, as occurs in association with diabet mellitus and chronic renal failure with impaired sodiu conservation and enhanced urea excretion.

Medullary Interstitial Osmolality

Osmotic diuresis caused by excessive sodium and ure excretion may be associated with nephrostomy drainag bladder decompression with a catheter in acute urinar retention, and the early stage of hypernatremia (befor volume depletion occurs from natriuresis and wate diuresis). Medullary interstitial hypertonicity is essenti to provide the gradient for free water reabsorptio under the influence of ADH. Therefore, if the medullar interstitium is not adequately hypertonic, as may occu through renal parenchymal damage, the urine will not b fully concentrated regardless of the plasma vasopressi levels. Thus, polyuria, with elimination of dilute urine may occur in acute and chronic tubulointerstiti nephritis as well as in other types of chronic ren

Table 1. Causes of polyuria

Causes	*Examples*
Expanded extracellular volume by free water intake	Compulsive water drinking; Heavy beer drinking
Excessive urinary solute load	Glucose load: diabetes mellitus; Mannitol load: mannitol infusion; Sodium load: excessive ingestion (e.g., as occurs in drowning)
Profound natriuresis accompanied by urea diuresis	Polyuric phase of acute tubular necrosis; Following relief of urinary tract obstruction; Chronic renal failure; Treatment with urea in SIADH
Impaired hypertonicity of medullary interstitium	Compulsive water drinking; Loop diuretic therapy; Acute and chronic tubulointerstitial nephritis
Reduced plasma vasopressin level	Partial and complete diabetes insipidus
Collecting tubule unresponsiveness to AVP (nephrogenic diabetes insipidus)	Congenital; Acquired Drugs: demeclocycline, lithium; Electrolyte and metabolic conditions: hypokalemia, hypercalcemia; Parenchymal renal disease: acute and chronic tubulointerstitial nephritis.

AVP, arginine vasopressin; SIADH, syndrome of inappropriate antidiuretic hormone

diseases. The hypertonic medullary interstitium may be diluted by chronic water loading as in compulsive water drinkers. Dilution may also occur by inhibition of sodium and chloride transport in the ascending thick limb of loop of Henle, which may account for the inability to concentrate urine in the water-deprived state induced by loop diuretics.

Plasma Vasopressin Level

Deficiency of AVP can result in a loss of 5 to 7 % of filtered water, which is equivalent to 9 to 12 liters of urine per day (170 L of glomerular filtrate in 24 hours). A typical example of AVP deficiency occurs in patients with complete or partial central diabetes insipidus, the causes of which include idiopathic, head trauma, and the post-hypophysectomy state.

Collecting Tubulur Responsiveness to AVP

In some individuals, even those with normal renal function, collecting tubule cells do not respond to ADH. This may be caused by defective receptor binding of ADH, as is seen in congenital nephrogenic diabetes insipidus. Acquired nephrogenic diabetes insipidus results from insensitivity of collecting tubule cells to ADH and can occur in a variety of renal diseases involving the medullary tubules and interstitium. Nephrogenic diabetes insipidus is also caused by a variety of drugs, including demeclocycline and lithium. Both agents inhibit adenylate cyclase and, hence, prevent production of cyclic adenosine monophosphate (cAMP), which is essential for the action of ADH.

DIABETES INSIPIDUS

Causes

Diabetes insipidus is a syndrome characterized by the elimination of abnormally large volumes of dilute urine (polyuria). It results from a deficiency in AVP release or in the action of AVP and can be caused by any of four fundamentally different defects of AVP. Thus, diabetes insipidus may be caused by the following:

- Impaired secretion of AVP, which is called neurohypophyseal diabetes insipidus
- Impaired renal response to AVP, which is called nephrogenic diabetes insipidus
- Excessive free water intake, causing impaired release of AVP, which is called primary polydipsia
- Increased metabolism of AVP by vasopressinase, as found in gestational diabetes insipidus.

Neurohypophyseal, or Central, Diabetes Insipidus

Primary impairment in ADH secretion results from extensive destruction of the AVP-producing magnocellular neurons in the posterior pituitary (neurohypophysis). This destruction can be idiopathic or can be caused by a variety of acquired or genetic diseases.

Causes

Acquired

The acquired causes of neurohypophyseal, or central, diabetes insipidus include surgery in the hypothalamic area; head trauma; various primary, metastatic, and hematologic malignancies; granulomas, and infections of the meninges or brain.

Genetic

The only clearly defined genetic form of neurohypophyseal diabetes insipidus is transmitted in a completely penetrant autosomal dominant mode. It appears to result from selective postnatal degeneration of AVP producing neurons and recently has been linked to mutations in the gene on chromosome 20 that codes for AVP - neurohypophysin II, the peptide precursor of AVP.

Idiopathic

The idiopathic form of neurohypophyseal diabetes insipidus resembles the genetic form in that the deficiency of AVP seems to be highly selective, occurs in the absence of any known cause, and, in some cases, appears to be caused by degeneration of magnocellular neurons in the neurohypophysis. The idiopathic form usually begins much later in life, however, and is not associated with a family history or with mutation in the coding region of the AVP-neurohypophysin II gene.

Pathophysiology

Destruction of the neurohypophysis causes a reduction in the amount of AVP secreted in response to the normal osmotic stimuli. This reduction in plasma AVP results in a decrease in urine osmolality and a reciprocal rise in the rate of urine flow. Along with increased urine flow, fluid intake increases to balance urine output, and dehydration is prevented. Thus, plasma AVP and urine concentration remain at levels that permit the development of symptomatic diabetes insipidus even though enough neurohypophysis remains to secrete adequate amounts of AVP in response to an abnormally intense stimulus, such as fluid deprivation. At this stage of response, the deficiency state can be classified as partial diabetes insipidus.

Partial diabetes insipidus may remain stable or may progress, with no AVP release in response to hypertonic dehydration. This state of complete unresponsiveness to release of AVP is called complete diabetes insipidus.

Patients with neurohypophyseal diabetes insipidus continue to exhibit usual diurnal variation in urine output. Thus, the rate of urine flow at night is approximately half that during the day, although both volumes are well above normal. Appreciable dehydration is rare in patients with neurohypophyseal diabetes insipidus so long a thirst perception is intact and there is access to fre water. However, hypernatremic dehydration may develo if additional losses of fluid occur through vomitin diarrhea, or inaccessibility to a water supply becaus of stroke or other impairments. The risk is highest f patients with complete diabetes insipidus because the cannot concentrate their urine regardless of the severit of their dehydration. Dehydration in diabetes insipidu is more likely to occur in youg children and in patien with damage to the thirst center.

Nephrogenic Diabetes Insipidus

Nephrogenic diabetes insipidus is characterized b reduced renal sensitivity to the antidiuretic effect of AV Thus, decreased urinary concentration, a slight increas in urinary flow, and mild hypertonic dehydration ma occur. If the renal insensitivity is minor, the rise in plasm AVP caused by dehydration may be adequate to overcom the defect and restore urinary concentration and flo toward normal. If the renal insensitivity to AVP is marke the increase in AVP secretion needed to overcom the degree of insensitivity may not be achieved befor hypertonic dehydration results in thirst and polydipsi Patients with nephrogenic diabetes insipidus also exhib the usual circadian variations in urine and are subje to almost the same risks of hypertonic dehydratio as those with neurohypophyseal diabetes insipidu The main difference between neurohypophyseal an nephrogenic diabetes insipidus is that no damage to th thirst mechanism is evident in patients with nephrogeni diabetes insipidus.

Lithium-induced Diabetes Insipidus

Lithium is a commonly used drug for bipola illness. Consequently, an increased number of ren consultations is obtained from psychiatric practitioner regarding a variety of renal problems observed i patients treated with lithium. The most common an probably most important adverse effect of lithium i polyuria. Total urine volume and osmolality in patient treated with lithium are similar to those in patients wit hypophyseal or nephrogenic diabetes insipidus. Sinc AVP does not decrease urine volume or increase urin concentration, the defect is tubular unresponsivenes to ADH and is similar to other causes of nephrogeni diabetes insipidus. In patients treated with lithium

ADH levels are elevated compared with those in control subjects. This finding confirms that ADH production is normal but that the collecting tubule is unresponsive to ADH. The vasopressin-resistant diabetes insipidus caused by lithium may be caused by a circulating factor that either binds ADH and makes it inactive or that causes the secretion of an inactive form, which competes with active ADH for receptor sites in the collecting tubules. In addition to this functional defect, chronic tubulointerstitial nephritis may occur in chronic lithium users, which can result in further impairment of urinary concentration and increase the polyuria caused by vasopressin-resistant diabetes insipidus.

Primary Polydipsia

Excessive water intake in patients with primary polydipsia decreases plasma osmolality and sodium concentration, which blunts release of AVP. This results in a water diuresis, which prevents the development of water intoxication. Patients with psychiatric disturbances may continue to have polyuria and polydipsia unless water intake is curtailed. Conversely, any attempt to reduce polyuria by administration of vasopressin will result in severe symptomatic hyponatremia because of water intoxication, which gives rise to central nervous system manifestations such as headache, confusion, coma, and even death. These patients can still concentrate their urine on water deprivation, although maximal concentrating capacity is frequently blunted.

Gestational Diabetes Insipidus

The signs and symptoms of gestational diabetes insipidus are associated with lower basal plasma osmolality and sodium levels than other types of diabetes insipidus. However, the symptoms remit soon after the placenta is delivered. Polyuria and polydipsia can appear in the third trimester or in the immediate post-partum period. Gestational diabetes insipidus is more common in the primigravida and may occur especially in women who develop preeclampsia or acute fatty liver of pregnancy. Thus, the association of transient diabetes insipidus with acute fatty liver of pregnancy appears more common than previously recognized.

Diabetes insipidus in pregnancy may be vasopressin-sensitive or vasopressin-resistant. The fundamental defect for gestational diabetes insipidus is excessive vasopressinase activity (produced in increasing amounts by placenta), causing inactivation of both endogenous and exogenous vasopressin. Histopathologic examination of the renal glomeruli from these patients may show glomerular lesions similar to those observed in women with preeclampsia.

POLYURIA OF HYPERCALCEMIA

There are several potential sites of action at which a drug or a physiologic disturbance such as elevated calcium levels may interfere with the urinary concentrating mechanism, causing polyuria. The impairment of urinary concentration in hypercalcemia could be caused by one or more abnormalities, including:

- A primary increase in water intake
- A reduced gradient for water permeability across the collecting tubules
- Decreased release of AVP
- Collecting tubule lack of response to AVP

An important mechanism appears to be an increase in medullary blood flow as a result of increased prostaglandin associated with hypercalcemia.

Diagnosis and Laboratory Testing

Standard Clinical Tests

The standard clinical tests are:

- Water deprivation test
- Response to exogenous vasopressin

These two tests can help with the differentiation among the three major causes of polyuria: central (neurohypophyseal) diabetes insipidus, nephrogenic diabetes isipidus, and primary polydipsia.

Water Deprivation Test

Procedure

The water deprivation test takes 6 hours and is done under strict medical supervision because some patients (e.g., compulsive water drinkers) with primary polydipsia may find access to water and continue to drink. The general procedure follows:

1. Body weight and urine osmolality and serum electrolyte measurements are obtained beore the test begins, and plasma vasopressin levels are drawn.
2. Weight should be recorded hourly. The test is discontinued if a patient loses more than 5% of the baseline body weight at any time during the test.

3. At the end of the test, body weight is again recorded, urine osmolality and serum electrolytes are measured, and plasma vasopressin levels are obtained. Additional serum electrolyte measurements may be obtained during the test, especially in patients with rapid weight loss. Weight loss accompanied by hypernatremia suggests severe polyuria, which is most consistent with complete central diabetes insipidus.

Evaluating Water Deprivation Test Results

In normal individuals, water deprivation increases urine osmolality to 800 to 900 Osm/kg. In patients with primary polydipsia (compulsive water drinkers), urine osmolality also increases substantially but may not reach the levels seen in controls. Urine osmolality may increase slightly or not at all from the baseline in patients with complete central and nephrogenic diabetes insipidus. However, in patients with partial central diabetes, AVP release may occur in response to plasma hypertonicity and permit some degree of urinary concentration to occur. Therefore, a slight or no increase in urinary osmolality from the baseline suggests either neurohypophyseal (complete central) or nephrogenic diabetes insipidus.

Therapeutic Vasopressin Test

The vasopressin test consists of subcutaneous injection of 5 U of aqueous Pitressin (Parke Davis, Morris Plains, NJ). In patients with central diabetes insipidus, urinary osmolality will promptly increase from 30 to 200%, depending on the severity of the deficiency. Less than a 10% increase in urinary osmolality will be noted in patients with nephrogenic diabetes insipidus or primary polydipsia.

Instead of conducting the cumbersome and protracted water deprivation test, a therapeutic test with vasopressin (or desmopressin) may be tried in the hospital setting, with the following outcomes:

- If desmopressin (or DDAVP; deamino-8-D-arginine vasopressin) at 2 to 4 μg subcutaneously every 12 hours for 2 days abolishes the polyuria and polydipsia without causing water intoxication, the odds are excellent that the paient has neurohypophyseal diabetes insipidus.
- If the polyuria is abolished, but causes a smaller or no reduction in polydipsia and results in the development of water intoxication (hyponatremia), the odds are great that the patient has primary polydipsia.
- No response is diagnostic of nephrogenic diabetes insipidus. Partial central diabetes insipidus at times can be difficult to distinguish from primary polydipsia because both entities variably respond to water deprivation with an increase of urinary osmolality, which further increases with administration of Pitressin.

Plasma AVP Measurement

Clinically, the cause of polyuria resulting from disorders of ADH release or ADH resistance (nephrogenic diabetes insipidus) can be identified by patient's response to administration of exogenous vasopressin. Determining plasma vasopressin levels is helpful, but the results take several days to obtain. Furthermore, the test is expensive.

Single AVP levels are not helpful in distinguishing central diabetes insipidus from primary polydipsia because the AVP level can be low in both conditions, especially if the sample is drawn before the water deprivation test is initiated. However, a paired sample drawn before and at the end of the water deprivation test can help the clinician differentiate between the two conditions. In patients with central diabetes insipidus, a slight or no rise in the AVP levels may be seen in the second sample, depending on the severity of the deficiency, whereas an appreciable rise in AVP levels may be seen in compulsive water drinkers. In patients with nephrogenic diabetes insipidus, plasma AVP levels may not change before and after the test.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) of the brain may help to distinguish between partial central diabetes insipidus and primary polydipsia. A normal hyperintense signal is noted in almost 98% of patients without sellar disease; however, the signal is absent in those with sellar disease. Hyperintense signals are therefore likely to be found in the patient with primary polydipsia but absent in patients with central diabetes insipidus. The pitfall is that the signal may be absent in patients with nephrogenic diabetes insipidus. Thus, MRI can be useful in distinguishing central diabetes insipidus from primary polydipsia but may not be helpful in differentiating central from nephrogenic diabetes insipidus.

Cautions in Testing

- The water deprivation test should be done during the day and under strict medical and nursing supervision.
- The water deprivation test, even under vigilant supervision, may demonstrate less than optimal urinary concentration in patients with primary polydipsia. This is because of medullary "wash out" (interference with the medullary concentrating mechanism) and a lack of hypertonicity. In these patients, the urinary concentration will increase more if the patient is administered protein and salt before the water deprivation test.
- Any preparation of vasopressin, either aqueous vasopressin or desmopressin, should be administered with caution in a patient with suspected primary polydipsia. Continuous drinking of water after vasopressin therapy could lead to water intoxication and acute symptomatic hyponatremia (confusion, headache, convulsions, etc.).

Summary of Diagnosis

- Excessive free water intake (compulsive water drinking), solute overload (diabetes mellitus), and chronic renal disease are common causes of polyuria and nocturia.
- Deficiency of AVP (complete central diabetes insipidus) gives rise to massive polyuria.
- Nephrogenic diabetes insipidus is another cause of polyuria.
- Patients with central diabetes insipidus exhibit the usual diurnal variation in urine output; the rate of urine flow at night is approximately half of that during the day, although both volumes are above normal.
- Patients with psychiatric disturbances may continue to have polyuria and polydipsia unless water intake is curtailed.
- Compulsive water drinkers can still concentrate their urine on water deprivation, although maximal concentrating on capacity is frequently blunted.
- The water deprivation test and response to exogenous vasopressin can help with the differentiation among central diabetes insipidus, nephrogenic diabetes insipidus, and primary polydipsia.

TREATMENT

Therapeutic options are directed at the cause of polyuria. If polyuria is caused by excessive excretion of osmotically active substances such as glucose, urea, or mannitol, treatment is directed to reduce excretion of these substances in the urine. For instance, treatment of diabetes mellitus with insulin or an oral hypoglycemic agent is essential to reduce glucosuria and minimize polyuria. Similarly, a low protein diet prescribed to patients with chronic renal failure helps to reduce nitrogen load and urea excretion.

Primary Polydipsia

Patients with primary polydipsia frequently have underlying mental disorders. The first step should be the treatment of the underlying psychiatric disorder(s), which may help curtail the compulsive water drinking. With reduced water intake, urinary concentration will increase over time.

Neurohypophyseal Diabetes Insipidus

Vasopressin is the treatment of choice for neurohypophyseal diabetes insipidus. Although various treatment regimens for complete and partial central diabetes insipidus are presented in Table 2, desmopressin is the safest and most effective, albeit the most expensive form of treatment. Development of significant hyponatremia is rare with desmopressin.

Pitressin in oil is effective and long-acting, but causes increased blood pressure and hyponatremia.

Chlorpropamide is another safe and effective oral therapy. When used alone or in combination with hydrochlorothiazide, it usually reduces urine output to asymptomatic, if not normal, levels even in patients with severe AVP deficiency. The antidiuretic effect is usually rapid in previously untreated patients, but it may take longer 7-10 days if the patient has been treated recently with pitressin or desmopressin. The mechanism of action is unclear, but it does not involve increased release of AVP. Hypoglycemia (in particular prolonged hypoglycemia) may occur, especially if chlorpropamide is used alone. If the drug is used in conjunction with hydrochlorothiazide, the hypoglycemic effect may be minimized.

Nephrogenic Diabetes Insipidus

Nephrogenic diabetes insipidus may be treated by desmopressin, any of the oral hypoglycemic agents listed in Table 2. The dosage and administration of each agent is similar to those used in the treatment of central diabetes insipidus.

Table 2. Treatment of diabetes insipidus

Medication	*Dose*	*Route*	*Onset*	*Duration*	*Comments*
Hormonal Therapy					
Vasopressin tannate (Pitressin in Oil) (arg & lys VP; 5 U/mL)	2-5 U	SC; IM	2-4 h	24-72 h	Emulsion must be shaken and warme before use. Vasoconstriction and smoot muscle contraction are common side effect
Synthetic vasopressin (lypressin; 50 U/mL)	5-10 U	Nasal spray	30-60 min	4-6 h	Replaced pituitary "snuff" because it i relatively nonallergenic and nonirritating
Desmopressin (DDAVP; 100 µg/mL)	5-20 µg	Nasal spray	30-60 min	12-24 h	Drug of choice for complete centr diabetes insipidus
Desmopressin (DDAVP; 4 µg/mL)	1-4 µg	SC	30 min	8-12 h	Also a good choice for central diabete insipidus, Hyponatremia may occur
Desmopressin (DDAVP; 0.1 mg tablet)	0.1-0.4 mg	PO	30 min	8-12 h	Mild increase in liver enzymes may occu Contraindicated in patients with live disease, Gastrointestinal symptoms ma occur
Adjunctive Therapy					
Chlorpropamide Diabinese (250 mg tablets)	100-500 mg/d	PO	2h	24-36 h	May be given as single dose; start at 10 mg; increase 1 tablet every 3-4 days expect hypoglycemia at doses over 50 mg/d; used only in partial central diabete insipidus
Hydrochlorothiazide Hydro DIURIL (50-mg tablet)	50-100 mg/d	PO	2-4 h	12-24 h	Usual thiazide side effects; can be used i central or nephrogenic diabetes insipidu

Adapted with permission from Singer I. The management of diabetes insipidus in adults. Arch Intern Med 1997; 157: 1293-30
Arg & Lys VP, arginine and lypressin (8-lysine) vasopressin; DDAVP, deamino-8-D-arginine vasopressin; IM, intramuscular; S subcutaneous; PO, by mouth

REFERRAL

Patients with polyuria, in whom the cause is not easily determined, should be referred to a nephrologist or an endocrinologist. If the cause of polyuria is determined and found to be central diabetes insipidus, an endocrinologist may be the appropriate consultant. A nephrologist may be the appropriate consultant for all other causes of polyuria.

Commonly Asked Questions

Why do I need to go to the bathroom so often day and night?

Frequent urination could be caused by insulin deficiency, caused in turn, by diabetes mellitus, or by vasopressin deficiency, caused in turn by diabetes insipidus. Insulin is released by the pancreas, whereas vasopressin is released by the pituitary gland, which is located at the base of the brain.

I am exhausted because I am up all night going to the bathroom. Is there anything you can do to help me?

Yes. Once we determine why you must go so often, you can be treated effectively and the number of your visits to the bathroom will steadily decrease.

Do I have to continue the treatment for the rest of my lif

Yes, however, convenient treatment regimens a available. For instance, for diabetes mellitus, a varie of oral agents are available as a substitute for insul injection, and pills or snuff can be used instead of injecti for diabetes insipidus.

Are there side effects from these drugs?

Yes, there are side effects. You and a family memb should be familiar with the side effects of the medicatio you are taking so that they can be recognized; if they occ report to your physician or hospital in case of emergen

(Male patient) I wake up a few times at night to go the bathroom and have difficulty passing water. Wh should I do?

Most likely your prostate gland is enlarged, which obstructing the urine flow. This condition can be treat medically or surgically.

KEY POINTS

- Three major causes of polyuria are central diabet inispidus, nephrogenic diabetes insipidus, a primary polydipsia.

- The water deprivation test for 12 hours and administration of exogenous vasopressin (5U aqueous pitressin subcutaneously) generally help to differentiate the three polyuric conditions.
- Plasma vasopressin levels measured before and after the water deprivation test can be helpful in differentiating between central and nephrogenic diabetes insipidus, but these measurements take several days to obtain, and therefore the test is not practical.
- Weight loss accompanied by hypernatremia suggests severe polyuria, which is most consistent with central diabetes insipidus.
- Hypernatremia generally does not occur in patients with central diabetes insipidus so long as the thirst center is intact and the patient is otherwise healthy.
- In lieu of the water deprivation test, if desmopressin given subcutaneously abolishes polyuria and polydipsia without producing water intoxication (hyponatremia), the odds are excellent that the patient has central diabetes insipidus.
- If desmopressin abolishes polyuria but causes a slight or no reduction in polydipsia and results in the development of water intoxication, the odds are great that the patient has primary polydipsia.

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10

Calcium and Phosphorus Metabolism Associated with Clinical Disorders in Pediatric and Adult Population

Rajendra Bhimma, Anil K Mandal

CALCIUM

In the healthy adult, calcium accounts for approximately 2 percent (1300g) of body weight. This makes it the most abundant electrolyte in the human body. The major reservoir of calcium in the body is the bones, storing 99 percent of total body calcium. The remainder is in teeth, soft tissue, and extracellular fluids.

Calcium absorption and regulation involve a complex interplay between multiple organ systems and regulatory hormones. The three predominant sources of calcium and targets for regulation are the bones, renal filtration and reabsorption, and intestinal absorption. Calcium and phosphate absorption in the gut is incomplete. Variations in intestinal absorption and release from bone, as well as urinary excretion, contribute to the regulation of calcium and phosphate balance.

Calcium in plasma exists in three fractions: approximately 40 percent of the plasma calcium is bound to albumin and is not filtered at the glomerulus; 50 percent is physiologically important ionic calcium (free Ca^{2+}) and is filtered; 10 percent is bound to sulfate, bicarbonate or phosphate. The major regulators of calcium levels are parathyroid hormone (PTH) and vitamin D, which target the bones, intestines, and kidney to increase serum calcium. Calcitonin plays a much smaller role and has the opposite effect of decreasing serum calcium by decreasing release of calcium from bone and decreasing reabsorption of calcium by the kidneys. Cyclically high levels of calcium suppress PTH release and thereby decrease levels of the active form of vitamin D by decreasing the activity of renal 1 alpha-hydroxylase.

Renal Handling of Calcium

The filtered calcium is reabsorbed throughout the nephron with about 200 mg being excreted in the urine per day on a regular diet. Approximately 80 to 85 percent is reabsorbed in the proximal tubule and medullary loop of Henle. This is predominantly passive transport. Passive calcium reabsorption in the thick ascending limb of the loop of Henle occurs via the paracellular pathway, a process that appears to be facilitated by a tight junction protein called paracellin-1.

The regulation of calcium excretion according to physiological needs occurs in the distal tubule and the adjacent cortical thick ascending limb of the loop of Henle and the connecting segment. In these segments, PTH and, to a lesser degree, vitamin D stimulate calcium absorption. PTH activates a hormone adenylate cyclase system, while vitamin D induces the production of calcium-binding proteins (calbindins) and potentiates the effect of PTH.

Although the kidney serves as the regulator of calcium flux, it has a limited capacity to handle large increases in the serum calcium levels. Bone remodeling on the other hand can engineer large but slower change in the serum calcium by a slow change in the balance between osteoblastic bone formation and osteoclastic bone reabsorption. PTH increases calcium entry through calcium channels in the apical membrane, although the mechanism by which it occurs is incompletely understood. It has been suggested that the primary effect of PTH is to increase the number of open chloride channels in the basolateral membrane. The ensuing loss of anionic chloride from the cell will hyperpolarize the cell membrane, thereby enhancing both the activity of voltage-dependent calcium channels in the luminal membrane and the gradient for passive calcium entry into the cell. A vitamin D-dependent calcium binding protein also appears to facilitate calcium uptake at the luminal membrane. PTH also stimulates enzymatic conversion of 25-hydroxyvitamin D to the active metabolic 1.25-dihydroxyvitamin D.

Regulators of Calcium Metabolism

The primary action of PTH is to increase serum calcium and decrease serum phosphorus by the following mechanisms:

- Directly causes rapid resorption of calcium from the bone into the plasma, elevating serum calcium both by directly stimulating the osteolytic calcium pump and by ostecoclast up-regulation.
- Directly causes renal tubular reabsorption of calcium in the loop of Henle and distal tubule.
- Inhibits phosphate reabsorption, as well as that of sodium, water, and bicarbonate in the kidney.
- Promotes renal conversion of 25-hydroxyvitamin D to the more active form 1,25-dihydroxyvitamin D by stimulating renal 1-alpha hydroxylase activity.

PTH is stimulated by increases in phosphate, decreases in calcium, adrenergic agents, magnesium, and certain vitamin D metabolites and is suppressed by hypercalcemia and high levels of 1,25-dihydroxyvitamin D.

Vitamin D in its active form of 1,25-dihydroxyvitamin D (also known as calcitriol or Rocaltrol®) increases serum calcium and serum phosphorus levels by the following mechanisms:

- Increases calcium and phosphate absorption from the intestines.
- Increases mineralization of bone, possibly by increasing intracellular transport of calcium ions and by increasing circulating concentrations of calcium and phosphate.
- Increases calcium reabsorption in the distal tubule of the kidney.
- Is inhibited by exogenous phosphate and corticosteroids.

Calcitonin causes an overall decrease in serum calcium by the following mechanism:

- Impairs bone osteolytic activity.
- Prevents osteoclast formation.
- Increases urinary excretion of calcium.

Other factors altering serum calcium include the following:

- Metabolic alkalosis, which causes an increase in tubular calcium reabsorption and a decrease in release of calcium from bone and enhances albumin-binding of calcium resulting in hypocalcemia.
- Phosphate-induced decrease of serum calcium levels and increase of PTH.
- Stimulation of osteoclasts by cytokines, such as tumor necrosis factor, interleukin-1, and interlukin-6.

Causes of Hypercalcemia

The causes of hypercalcemia vary by age and other related factors, which include hypocalciuria or hypercalciuria.

Neonates and Infants

Neonatal Primary Hyperparathyroidism

This is due to parathyroid gland hyperplasia. It presents in early infancy with malaise, constipation, and vomiting. Serum biochemisty shows elevated calcium and PTH concentrations with a low serum phosphate level. It is often associated with aminoaciduria. Radiological features include rarification of bones with pathological fractures.

The pathophysiology of this condition is due to a homozygous inactivating mutation in a calcium-sensing receptor. Management involves radical parathyroidectomy. Emergency management for symptomatic patients involves hydration with isotonic sodium chloride solution and forced diuresis using a loop diuretic. If hypercalcemia is not corrected, administration of subcutaneous calcitonin (1 to 4µg/kg) may be considered.

Familial Hypocalciuric Hypercalcemia (FHH)

This condition may begin in infancy or childhood. It is inherited as an autosomal dominant heterozygous mutation of the calcium receptor-sensing gene. The disease is best characterized as an abnormality in the physiological set point of serum calcium concentration. The infant or child is generally asymptomatic, but the elevated calcium level is inappropriate for the clinical status. The PTH concentration, though in the reference range, is inappropriately high for the degree of hypercalcemia. Other biochemical abnormalities include a decreased or normal serum phosphorus level, normal levels of alkaline phosphatase, and normal serum 25 hydroxyvitamin D with an appropriate level (to the PTH) of 1.25-dihydroxyvitamin D. Serum calcium levels rarely exceed 14 mg/dL; urine calcium excretion is decreased to less than 200 mg per day, but the level of urine cyclic adenosine monophosphate (cAMP) is normal. The urinary calcium to creatinine ratio (both values in milligrams) is 0.03 or less. The serum magnesium level is elevated in about 50 percent of cases. Radiological findings are normal. Diagnostic clues apart from the biochemical findings above include a family history and absence of the autoimmune polyglandular syndromes. Asymptomatic patients do not require specific treatment. Symptomatic patients, usually in the neonatal period, are managed as neonatal primary hyperparathyroidism. Parathyroidectomy is not helpful.

Williams Syndrome

The genetic defect for Williams syndrome is a heterozygous microdeletion of 7q11.23 and encompasses the elastin gene. Rarely it may involve a defect of chromosome 11[del (11)(q13.5q14.2)] or even chromosome 22[(r(22) (p11—q 13)]. The usual presentation is transient neonatal hypercalcemia, perhaps secondary to increased sensitivity to vitamin D. Williams described infants with supravalvular aortic stenosis, peculiar faces ("elfine like"). and hypercalcemia during the first year of life. Two thirds of these infants may be small for gestational age and many are postdate. Facial abnormalities include structural asymmetry, temporal depression, flat malae with full cheeks, microcephaly, epicanthic folds, lacy or stellate irises, a short nose with a full philtrum, an arched upper lip with a fuller lower lip, and small maloccluded teeth. These children are usually affable and have a hoarse voice. Other abnormalities include various forms of congenital heart defects and stenosis of the renal, mesenteric, and celiac arteries. Hypercalcemia usually does not persist beyond the first year of life, but hypercalciuria persists throughout childhood and adolescence. Renal abnormalities include urinary frequency, daytime urinary incontinence and hypoplasia or dysplasia of the kidney. Treatment is directed toward the associated abnormalities, especially hypertension and cardiovascular anomalies. An almost calcium-free diet and restriction of vitamin D intake are encouraged for normalization of serum calcium levels. Hydrocortisone at 10 - 25 mg/kg/day is sometimes helpful.

Idiopathic Infantile Hypercalcemia

This condition was first reported by Lightwood in the early 1950s in England and was ascribed to vitamin D intoxication. Several cases have been reported thereafter where maternal vitamin D intoxication has not been an issue. In several children, an elevated level of N-terminal PTH-related protein was demonstrated at the time of hypercalcemia. Affected infants generally have higher serum calcium levels than those with Williams syndrome, increased thirst, and symptomatic hypercalcemia. Other associated manifestations include hypertension, strabismus, inguinal hernias, disordered posture, kyphosis, radioulnar stenosis, dislocated patellae, and hyperacusis. Treatment is directed to reduce serum calcium level as described above. Hypercalcemia usually resolves spontaneously after age 12 months.

Hypophosphatasia

Infantile *hypophosphatasia* is a disease of bone mineralization in which serum alkaline phosphatase activity is absent or significantly diminished. It presents with clinical and radiological features of rickets. The condition may result in fetal death. Biochemical abnormalities include hypercalcemia, hypercalciuria, and increased excretion of urinary phosphoethanolamine.

Secondary Hyperparathyroidism

This is a neonatal response to maternal hypocalcemia with similar symptoms to primary hyperparathyroidism, except that the child undergoes progression from hypocalcemia to normocalcemia to hypercalcemia quickly after birth. PTH levels are generally elevated. During the first few months, the parathyroid glands and skeletal lesions regress; therefore, only symptomatic nonsurgical treatment is required.

School-age Children

Autosomal dominant hereditary hyperparathyroidism

This is a rare condition in older children and may be asymptomatic. Symptomatic children present with personality changes. The condition is characterized by an inappropriately high level of PTH for the degree of hypercalcemia in all patients. Serum and urine calcium are high. Serum phosphorus is low and associated with high urinary phosphorus. Other biochemical abnormalities include an elevated nephrogenous cAMP levels and mildly elevated 1,25 $(OH)_2D$ levels. Radiological findings of osteitis fibrosia cystica may be present. Treament is total parathyroidectomy.

Multiple Endocrine Neoplasia (MEN)

MEN type 1, i.e., Wermer syndrome, is a rare autosomal dominant condition presenting with hyperparathyroidism, pancreatic tumors, and pituitary tumors. Usually hyperparathyroidism is the presenting feature of MEN type 1 in the majority of patients. Patients may have asymptomatic, hypercalcemia. All four glands are diffusely hyperplastic, and there may be nodule formation. Management is subtotal parathyroidectomy. Genetic linkage analysis is now availbale and has greater than 95 percent predictive accuracy.

Adults

Primary Hyperparathyroidism

Primary hyperparathyroidism (HPT) is the most common cause of hypercalcemia in adults, accounting for more than half of the cases in the general population. Hypercalcemia is mainly due to increased bone resorption, but other factors for hypercalcemia include increased intestinal absorption of calcium due to elevated levels of 1-25 $(OH)_2D_3$ and decreased renal clearance of calcium due to a direct effect of PTH and volume depletion. Slightly less than half of the patients are asymptomatic; in the remaining patients, nephrolithiasis and moaning and groaning from the bone pain are the common reasons for consultation.

Seventy-five to 80 percent of the patients with HPT have a single adenoma. Hyperplasia of all four parathyroid glands is found in 20 to 25 percent of the patients and parathyroid carcinoma accounts for less than 1 percent of the cases. In rare instances, HPT may be associated with other endocrinologic abnormalities, such as in the multiple endocrine adenomatosis (MEA, types 1 -pancreatic and pituitary tumors; and 2a -pheochromocytoma and medullary carcinoma of the thyroid).

Secondary Hyperparathyroidism

HPT secondary to gastrointestinal or renal disease usually is not associated with elevated calcium levels. Occasional cases of hypercalcemia in this setting were referred to in the past as "tertiary HPT." They are the results of resetting of the set point for PTH suppression. Hypercalcemia may develop after renal transplantation due to persistent hyperplasia of parathyroid glands. A similar mechanism probably accounts for the hypercalcemia seen during the recovery phase of acute renal failure due to rhabdomyolysis. In this condition, massive deposition of Ca in the necrotic muscular tissue leads to severe hypocalcemia and stimulation of PTH production during the oliguric phase. Release of the calcium into the circulation and persistently high levels of PTH during the recovery phase cause hypercalcemia. Hypercalcemia in the recovery phase of rhabdomyolysis may also be due to elevated levels of 1-25 $(OH)_2D_3$. Hypercalcemia in hemodialysis patients is commonly due to vitamin D therapy.

Malignancy

Malignancy is the second most common cause of hypercalcemia in the adults. Breast and lung carcinoma are most frequently associated with hypercalcemia, followed by multiple myeloma. Malignancies associated with hypercalcemia in children include: nonHodgkin's or Hodgkin's lymphoma, Ewing sarcoma, neuroblastoma, rhabdomyosarcoma with metastases to breast or bone marrow,, and ovarian small cell carcinoma in adolescents. Malignancy may cause hypercalcemia by lytic bone metastases, production of ectopic PTH, and PTH-related peptide (PTH-rP). Although this ectopic PTH is immunologically different from PTH, its biological activity is very similar to that of PTH. Eight pretreatment levels of serum PTH-rP may predict the effect of therapy, very high levels ($\geq$ 12 pmol/L) being associated with a poor response. Other mechanisms include production of prostaglandins by tumors and release of an osteoclastic-activating factor by lymphocytes. This has been demonstrated in multiple myeloma and lymphomas. Increased production of 1-25 $(OH)_2D_3$ has also been found in lymphomas. Less well defined, malignancy-related hypercalcemic mechanisms are tumor-produced growth factors. Finally, several reports have recently drawn attention to the association of primary HPT with cancer, suggesting that this should be ruled out in every hypercalcemic patient with malignancy.

Calcitriol-mediated Hypercalcemia

A distinct syndrome of calcitriol-mediated hypercalcemia is seen in patients with Hodgkin's or nonHodgkin's lymphoma as well as sarcoidosis. The syndrome is characterized by:

1. Hypercalcemia
2. Increased intestinal absorption of calcium
3. Normal or slightly elevated serum phosphorus level
4. Absence of renal phosphate wasting
5. Elevated serum calcitriol level
6. Increased urinary excretion of calcium
7. Suppressed PTH and PTHrP levels
8. Normal nephrogenous cAMP

Extrarenal production of calcitriol appears to be the underlying defect in Hodgkin's or nonHodgkin's lymphoma, although it is unclear whether the lymphoma cells or infiltrating host monocytes and macrophages are the primary source. There is some evidence that other osteolytic factor, such as interleukin-1 and tumor necrosis factor along with calcitriol, may exacerbate hypercalcemia in these malignancies.

Acute Immobilization

Immobilized patients may develop hypercalcemia, which is reversible after mobilization. This condition is particularly common in patients with high bone turnover, such as growing children and in Paget's disease, but its mechanism is not fully understood. PTH levels have been found to be low or high.

Hyperthyroidism

Hypercalcemia may be present in up to 50 percent of hyperthyroid patients. The mechanism of increased bone resorption is related to a direct effect of thyroid hormone mediated by increased sensitivity of β-adrenergic receptors. PTH and vitamin D levels are decreased.

Pheochromocytoma

Hypercalcemia may be present in this condition as a consequence of catecholamine-stimulated PTH secretion. Catecholamines, however, may also directly enhance bone resorption.

Lithium Carbonate

Patients treated with lithium may develop hypercalcaemia associated with elevated levels of PTH.

Vitamin A Intoxication

Excess vitamin A may induce hypercalcemia by increasing bone reasborption. It should be noted, however, that most vitamin A containing preparations also contain vitamin D, suggesting that hypercalcemia may be due to a combination of excessive intake of vitamin A and vitamin D.

Vitamin D

Hypercalcemia due to excessive intake of vitamin D may occur in patients treated for rickets, osteomalacia, or hypoparathyroidism. Vitamin D intoxication is also the cause of the so-called "idiopathic hypercalcemia of infacy" described mainly in Great Britain in the 1950s and rarely seen today. Large doses of vitamin D are required for the control of serum phosphorus levels in dialysis patients and the early postoperative period after parathyroidectomy.

Granuloma

Granulomatous disorders causing hypercalcemia include sarcoidosis, tuberculosis (TB), Wegener's disease, cat-scratch disease, berylliosis, and *Pneumocystis jiroveci* pneumonia. In patients with sarcoidosis, 30 to 50 percent manifest hypercalcemia and 20 to 30 percent demonstrate isolated hypercalciuria. The mechanism of hypercalcemia in these disorders is thought to be due to the expression of 25-hydroxyvitamin D-1 a-hydroxlase or another mixed function microsomal oxidase capable of transforming 25 hydroxyvitamin D. This leads to unregulated production of 1,25 $(OH)_2D$ and consequent hypercalcemia. Treatment of the primary disease leads to a stabilization of serum calcium levels.

Medication and iatrogenic causes of hypercalcemia include:

Thiazide Diuretics
Lithium
Tamoxifen
Oral contraceptives
Calcium-containing antacids
Theophyllin
Vitamin A in high dose such as retinoid therapy for acne
Vitamin D intoxication
Total parenteral nutrition
Oral dietary phosphate deficiency

The use of thiazide diruretics may be associated with elevated calcium levels mainly due to decreased renal excretion of calcium. This is related to a direct effect of thiazide on tubular transport and is also a consequence of volume contraction. This response requires the presence of PTH, and clinically important hypercalcemia is only seen when there is an underlying facilitating condition, such as primary HPT, increased ingestion of calcium, or lithium treatment.

Renal Transplant Recipients

Hypercalcemia occurs in 10 to 30 percent of renal transplant recipients, most often caused by persistent hyperparathyroidism in these patients. However, a low to normal PTH level and virtually undetectable levels of parathyroid related protein (PTHrP) were reported in a patient who had recurrent hypercalcemia for seven years. An elevated level of 1,25-dihydroxyvitamin D_3 (calcitriol) led to the diagnosis of an underlying lymphoma in this patient. The possibility of an underlying lymphoproliferative disorder, therefore, should be considered in differential diagnosis of hypercalcemia in renal transplant patients. Also, elevated levels of 1,25-dihydroxyvitamin D, should be a key indication for considering underlying nonHodgkin's lymphoma, which is common in transplant patients.

Milk-Alkali Syndrome

Milk-alkali syndrome had almost vanished but has surged again with the growing popularity of the use of calcium carbonate as an antacid or as calcium supplementation to prevent osteoporosis. A history of excessive intake of calcium-containing products and heavy consumption of dairy products, along with complete reversal of hypercalcemia, metabolic alkalosis and renal failure substantiated a diagnosis of milk-alkali syndrome.

Normocalcemic Hypercalciuria

Hypercalciuria is defined as urinary excretion of more than 250 mg of calcium per day for women and for more than 275 to 300 mg calcium per day for men while on a regular unrestricted diet. Hypercalciuria is the most common identifiable cause associated with calcium kidney stone disease. The most common types of clinically significant hypercalciuria are: absorptive, reabsorptive, and renal leak hypercalciuria.

Absorptive Hypercalciuria

This is found in about 50 percent of all calcium stone formers and is caused by an increase in the gastrointestinal absorption of calcium, overly aggressive vitamin D supplementation or excessive ingestion of calcium-containing foods (milk-alkali syndrome). Serum calcium levels are elevated with appropriately decreased PTH levels. There are three types of absorptive hypercalciuria: Type 1, 2, and 3. Type 1 is relatively uncommon and is usually unresponsive to dietary modifications. Type 2 is the most common variety that usually responds to moderate dietary restriction of calcium. Type 3 is due to renal phosphate leak. Essentially this is an absorptive vitamin-D dependent hypercalciuria due to an inappropriate vitamin D-3 activation from hypophosphatemia.

Resorptive Hypercalciuria

This condition is typically found in hyperparathyroidism and is due to loss of calcium from the body's normal stores in the bony skeleton.

Renal Leak Hypercalciuria

This is due to a specific defect in the kidneys that allows excessive obligatory urine calcium excretion regardless of serum calcium levels, body stores of calcium, or calcium ingestion. The urinary calcium/creatinine ratio is >2.0. The resultant mild hypocalcemia leads to secondary hyperparathyroidism.

It is important to note that the different types of hypercalciuria often overlap and exact differentiation is often unnecessary, as it does not influence therapy. Other conditions resulting in hypercalciuria include Bartter's syndrome, hyperprostaglandin syndrome, distal renal tubular acidosis, juvenile chronic arthritis, furosemide therapy, corticosteriod therapy, prolonged immobilization, and Dent's disease.

Symptoms of Hypercalcemia

Symptoms of hypercalcemia are often related to the underlying cause for hypercalcemia, the time course for the development of hypercalcemia, the severity of hypecalcemia, and intercurrent medical conditions. Hypecalcemia generally gives rise to neuromuscular, renal, and gastrointestinal manifestations. When serum calcium concentration rises above normal, the nervous system is the first organ system that is depressed and the reflex activities of the central nervous system become sluggish. The depressive effects of the central nervous system, such as confusion or altered mental state, manifests when total serum calcium level rises above 12 mg/dL, and they become more marked when the level rises to or above 15 mg/dL. When the calcium level is above 17 mg/dL, the patient is poorly responsive. Myoclonic jerks, generalized seizures, and coma may occur. Elevated calcium dcreases the Q-T interval of the heart and causes constitpation, loss of appetite, and nausea and vomiting because of decreased cotractility of smooth muscles of the gastrointestinal tract. In the elderly or critically ill patients, significant cognitive impairment may be seen with mild degrees of hypercalcemia. Marked dehydration and profound mental status changes accompany severe degrees of hypercalcemia (>15 mg/dL). Nephrolithiasis, peptic ulcer disease, and joint manifestations suggest primary hyperparathyroidism as the cause of hypercalcemia.

An increasingly recognized presentation of hyperparathyroidism, particularly in the elderly population, is severe hypercalcemia. In a study of 111 hypercalcemic hyperparathyroid patients found in an urban population of one million people in the United Kingdom, 14 subjects presented with acute hypercalcemic syndrome. The majority of patients with primary hyperparathyroidism have long-standing hypercalcemia, very large parathyroid adenomas, radiographic evidence of osteitis fibrosa cystica (50 percent), and a history of nephrolithiasis (60 percent). Osteitis fibrosa cystica is virtually never seen in hypercalcemia associated with malignancy. Acute hypercalcemic syndrome develops in assocation with severe hypercalcemia caused by malignancy or primary hyperparathyroidism. Patients with malignancy-associated hypercalcemia are usually symtomatic, and hypercalcemia adds significantly to their morbidity and mortality. More often, individuals with known malignancy are diagnosed with hypercalcemia during the course of the disease. The symptoms of hpercalcemia may masquerade as symptoms of the undelying malignancy or its therapy. For example, weight loss, anorexia, muscle weakness, constipation, and altered metal status are attributed to fulminating cancer. Impaired mental function, lethargy, and disorientation may be thought to be caused by narcotic analgesics or anxiolyti therapy, but, in fact, may be caused by hypercalcemia Hypercalcemic crisis is characterized by severe menta state changes, dehydration, and acute renal failure, which may be the first clinical manifestations of hypercalcemia associated with malignancy: In general, the higher the level of serum calcium, the more likely that malignancy is the cause for hypercalcemia.

Diagnosis

The differential features of primary hyperparathyroidism versus hypercalcemia of malignancy ars summarized in Table 1.

Summary of Diagnosis

1. PTH, in combination with vitamin D, is the principal regulator of serum calcium concentration. Dehydration is an important factor in the pathogenesis of hypercalcemia by means of its enhancing proximal tubular reabsorption of calcium and reduced urinary excretion.
2. Hypercalcemia is the most common metabolic complication of cancer.
3. The malignant neoplasms most commonly associated with hypercalcemia include carcinoma of the lung and breast, squamous cell carcinomas, hematologic malignancies, and renal cell carcinoma.
4. PTHrP plays a dominant role in the pathogenesis of humoral hypercalcemia of malignancy. The

Table 1. Differential diagnosis of two major causes of hypercalcemia

Features	*Primary Hyperparathyroidism*	*Malignancy*
Duration	Long history	Short history
Symptoms	Bone pain, renal stones common. Rarely, symptoms of hypercalcemia	Symptoms related to hypercalcemia: cognitive dysfunction, vomiting, constipation, renal failure
Intact PTH level	Elevated	Normal or low
PTHrP (n = 2.7 pmol/L)	Normal (95%)	Elevated (82%) without detectable metastatic bone disease
Serum calcitriol level	Normal	Elevated in Hodgkin's or nonHodgkin's lymphoma
Elevation of serum urea nitrogen	Uncommon	Common (mostly due to dehydration)
Urinary cAMP	Elevated	Suppressed
Glucocorticoid suppression test (prednisone 40 mg TID) for 2 days	No effect	Effective in decreasing serum calcium (breast cancer, lymphoma, myeloma)

PTH, parathyroid hormone; PTHrP, PTH-related protein.

stimulation of increased osteoclastic bone reabsorption by PTHrP is a principal feature of hypercalcemia of malignancy.

5. A distinct syndrome of calcitriol-mediated hypercalcmia is seen in patients with Hodgkin's or nonHodgkin's lymphoma.
6. Marked dehydration and profound mental status changes are common presenting features of severe hypercalcemia (serum calcium >17 mg/dL).

Treatment of Hypercalcemia

General measures include:

1. Hydration
2. Avoidance of calcium and vitamin D intake.
3. Identification of the underlying cause of hypercalcemia

Specific measures include:

1. Inhibiting bone resorption
2. Increasing renal sodium and calcium excretion
3. Decreasing intestinal absorption of calcium by suppressing vitamin D metabolism
4. Treating the underlying cause

Hydration

Because ECF volume depletion aggravates hypercalcemia by stimulating excessive reabsorption of calcium through the renal tubules, hydration is the essential first step to offset this process. Hydration can be accomplished with normal saline or normal saline in 5 percent dextrose in water. Fluid can be administered at a rate of 100 ml/hour or up to 150 ml/hour depending on the extent of blood pressure, skin turgor and mental state changes.

Calcium Diuresis

Calcium is co-transported with sodium; hence, inhibition of sodium reabsorption with a loop diuretic will result in inhibition of calcium reabsorption. Loop diuretics, such as furosemide, ethacrynic acid, or bumetanide, can inhibit reabsorption of up to 15 percent of filtered sodium in the ascending thick limb of loop of Henle. In so doing, a loop diuretic can promote urinary excretion of calcium up to 800 or even 1000 mg/day.

Calcium diuresis with a loop diuretic is recommended after ECF volume is somewhat repleted as evident from increase of blood pressure and urine output. There is no set dosage regimen of a loop diuretic; however, 40-mg intravenous bolus every 12 hours may be considered safe. Severe volume depletion accompanied by hyponatremia, hypokalemia, and hypomagnesemia may develop after repeated administration of high dose of a loop diuretic. These electrolyte disorders may result in cardiac arrhythmia and could prove dangerous, particularly in elderly patients with hypercalcemia. Therefore, serum electrolytes should be monitored twice daily at 6 am and 6 pm during the course of treatment with a loop diuretic. Urinary volume should be measured hourly. Fluid and electrolytes should be replaced in quantities appropriate to avoid volume depletion and electrolyte disorders. Rapid development of hyponatremia could lead to cerebral edema and convulsions; hypokalemia and hypomagnesemia could lead to dangerous cardiac arrhythmias, especially in those with underlying heart disease. Hypophosphatemia may develop and could lead to myopathy and rhabdomyolysis.

Inhibit Osteoclastic Bone Reabsorption

The principal pathophysiologic alteration in severe hypercalcemia is enhanced osteoclastic bone reabsorption. Therefore, the cornerstone of therapy in hypercalcemia is to inhibit osteoclastic bone reabsorption.

The following agents are effective to inhibit bone resorption:

- Calcitonin
- Biphosphonates
- Plicamycin (mithramycin)
- Gallium

Calcitonin is the most rapidly acting agent; it acts within minutes of its administration, decreasing the release of skeletal calcium, phosphorus, and hydroxyproline. In addition, calcitonin's action of decreasing renal tubular calcium reabsorption may, in part, explain its rapid onset of action. In doses of 4 IU/kg of body weight intravenously, subcutaneously, or intramuscularly every 6 to 12 hours, calcitonin rapidly lowers serum calcium. Administration of glucocorticoids in combination with calcitonin may prolong the action of calcitonin. Tachyphylaxis often develops and is a distinct disadvantage for repeated use of calcitonin. However, calcitonin's lack of toxic properties has a distinct advantage over other agents. Nevertheless, it causes minor, though usually transient, side effects, including nausea, abdominal cramps, flushing, and allergic reactions.

Biphosphonates (Diphosphonates)

The biphosphonates are analogs of pyrophosphate. The first-generation biphosphonate is etidronate (EHDP). A new generation of aminobiphosphonates includes pamidronate (ADP). These drugs have high affinity for hydroxyapatite of bone, especially in areas of bone turnover, such as those that occur at metastatic lesions. These bone-seeking biphosphonates are stable in the body, because phosphatase enzymes cannot hydrolyze their central carbon-phosphorus-carbon bond. Concentrated in areas of high bone turnover, the biphosphonates are taken up by osteoclasts and inhibit osteoclast action. Biphosphonates must be given intravenously to be effective in hypercalcemia.

Etidronate (EHDP)

Given in doses of 7.5 mg/kg/ day intravenously for 3 days normalizes serum calcium in 30 to 40 percent of patients. In some cases, continuation of oral EHDP after intravenous therapy may control hypercalcemia. At sustained oral doses of 25 mg/kg/day for more than 6 months, EHDP causes a mineralization defect.

Pamidronate (ADP)

ADP is extremely potent in inhibiting osteoclast-mediated skeletal reabsorption, yet does not cause mineralization defect. The efficacy, dose-response relationship, and safety of 30 mg, 60 mg, and 90 mg of a single, intravenous 24-hour infusion of ADP for the treatment of moderate to severe hypercalcemia of malignancy were studied. Serum calcium corrected for albumin, urine hydroxyproline, and urinary calcium excretion, and serum PTH levels were determined before and after ADP therapy. Serum calcium normalized in 40 percent of patients who received 30 mg, in 61 percent of patients who received 60 mg, and in 100 percent of patients who received 90 mg ADP. Usually 90 mg of pamidronate is mixed in a liter of normal saline and infused for 24 hours. The decrease in the serum calcium level happens in parallel iwith decreased osteoclastic skeletal resorption as evidenced by a decrease in urinary calcium and hydroxyproline excretion. Clinical improvement, including mental well being and increased appetite, is parallel to the fall in serum calcium, whether patients received 30 mg, 60 mg, or 90 mg of ADP. Side effects included: low-grade fever, asymptomatic hypocalcemia, hypophosphatemia, and hypomagnesemia. Esophageal ulceration is uncommon. Thus, ADP has a pharmacologic profile similar to that of EHDP, but ADP is more potent and remains effective over a longer time. In hypercalcemia of malignancy, ADP has an advantage over other agents that a single dose of ADP 90 mg intravenously provides a durable response.

Plicamycin (Mithramycin)

Plicamycin, derived from an actinomycete of the genus *Streptomyces,* is a tumoricidal antibiotic. Marked hypocalcemia was observed when plicamycin was administered at 50 μg/kg for 5 consecutive days. Plicamycin localizes in areas of active bone resorption and has been shown to directly inhibit bone resorption in vitro. Urinary calcium and hydroxyproline excretion decrease in patients treated with plicamycin. Plicamycin may also inhibit renal tubular reabsorption of calcium. Plicamycin must be administered by intravenous infusion. Doses of 15 to 25 μg/kg over 4 to 24 hours plicamycin lowers serum calcium within 24 to 48 hours. Total serum calcium is restored to normal within 48 hours in approximately 75 percent of patients. If serum calcium does not normalize within 48 hours, a second dose should be administered. An alternative treatment schedule consists of intravenous infusion of 15 to 25 μg/kg plicamycin for 3 to 4 consecutive days. Plicamycin has cumulative toxic effects and is less potent than the aminobiphosphonates. Thrombocytopenia associated with hemorrhage, renal insufficiency, and proteinuria may occur. Potential nephrotoxicity of plicamycin should preclude its use when there is moderate impairment of renal function.

Gallium Nitrate

Gallium nitrate is effective in hypercalcemia of malignancy. Normocalcemia, sustained for a mean period of 11 days, can be achieved in approximately 75 percent of patients treated with 200 mg/m^2 of gallium nitrate infused over 5 days. Gallium exerts greater efficacy compared to either calcitonin and EHDP. The major concern with gallium is renal function impairment.

Glucocorticoids

Glucocorticoids are the most effective agents used in hypercalcemia associated with elevated 1, 25-dihydroxyvitamin D_3 (calcitriol) and normal to low PTH and PTHrP levels. Glucorcorticoids are the most effective inhibitors of calcitriol production. Glucocorticoids are given in the form of prednisone

60 mg orally daily for 5 to 7 days. Thereafter, the dose will be tapered to a maintenance dose of 10 to 20 mg daily or on alternate days. Lower dosages and alternate-day schedules are effective in the hypercalcemia of granulomatous diseases. Side effects are uncommon with lower dosages or alternate-day schedules.

Calcimimemetic Agents

Presently, the only calcimimetic agent available for clinical use is cinacalcinet (Sensipar®). The agents act allosterically to increase the sensitivity of the calcium sensing receptor (CaSR) in the parathyroid gland to calcium. The CaSR is the principal factor regulating parathyroid gland PTH secretion and hyperplasia. Thus this group of agents offer a complementary and potentially synergistic mechanism with Vitamin D analogues that target the vitamin D receptor. Whereas active vitamin D analogues increase circulating fibroblast growth factor (FGF)23 concentrations, cinacalcinet used with lower doses of vitamin D reduces it.

Presently the main indications for the use of calcimimetics is in patients with severe hypercalcemia unresponsive to vitamin D analogues such as those with severe secondary hyperparathyroidism secondary to end stage kidney disease on dialysis, and in patients with parathyroid carcinoma. The use of these agents in patients with primary hyperparathyroidism has also been evaluated but presently this is not standard of care.

Phosphate

Phosphate given intravenously has a dramatic effect in severe hypercalcemia. Phosphate therapy leads to a decline in urinary and fecal excretion of calcium. Calcium kinetic studies show a rapid disappearance of calcium from the circulation within minutes of beginning a phosphate infusion. Calcium-PO product precipitates in the skeleton, kidneys, soft tissues, and heart. Intravenous phosphate is an effective treatment of severe symptomatic hypercalcemia in hypophosphatemic individuals but should be used with caution in normophosphatemic patients because it may cause hyperphosphatemia. The dose is 3.1 gm of phosphate by intravenous infusion for 24 hours. Hypercalcemia accompanied by hypophosphatemia, which occurs in primary hyperparathyroidism, may be treated with oral phosphate. Phosphate therapy carries a risk of sustained hyperphosphatemia in the presence of renal insufficiency.

Dialysis

Hemodialysis with no or low calcium dialysate is recommended in severe symptomatic hypercalcemia (hypercalcemic crisis) associated with moderate to severe renal failure, such as that seen in multiple myeloma. Calcium may be removed by hemodialysis to the extent of 250 mg per hour. Hemodialysis is not recommended for hypercalcemia of malignancy that has given rise to chronic urinary tract obstruction and chronic renal failure. In such cases, only palliative treatment with fluid, pamidronate or plicamycin (mithramycin), can be recommended. Unilateral or bilateral nephrostomy can be done to relieve azotemia and provide symptomatic relief.

Treatment of the Cause

Despite advances in therapy for hypercalcemia, the treatment of primary hyperparathyroidism is most often a surgical procedure. Medical management, beyond stabilization in preparation for surgery, has virtually no role in the management of primary hyperparathyroidism. Hypercalcemia for malignancy warrants tumor-specific chemotherapy and/or radiation therapy that should be supplemented by adjuvant treatment of hypercalcemia.

Pregnancy

Since the treatment of asymptomatic hyperparathyroidism itself is controversial, it is even more difficult to define the treatment plan for an asymptomatic pregnant woman who has primary hyperparathyroidism. However, a recent consensus panel has recommended that young patients with asymptomatic hyperparathyroidism should be treated surgically. The preferable period for surgical treatment is in the second trimester. Whether a patient is treated medically or surgically in these situations, the pregnancy should be considered high risk. The neonate should be monitored carefully for signs of hypocalcemia or impending tetany. If the mother is treated medically to term (or if spontaneous or elective abortion occurs), she should be monitored for hyperparathyroid crisis postpartum. Sudden worsening of hypercalcemia can result from the loss of the placenta and dehydration. The diagnosis of hyperparathyroidism should be suspected during pregnancy if the following conditions exist:

- Clinical symptoms or signs, especially nephrolithiasis or pancreatitis
- Hyperemesis beyond the first trimester
- History of recurrent spontaneous abortions or stillbirths or neonatal deaths
- Neonatal hypocalcemia or tetany or a total serum calcium concentration greater than 10.1 or 8.8 mg/dL during the second or third trimester, respectively.

Prevention

Good hydration is the vital preventive measure, because dehydration aggravates hypercalcemia. Biphosphonates or corticosteroids given orally on a long-term basis may mitigate the severity of hypercalcemia. Intake of calcium-rich foods, such as dairy products, should be limited. Multivitamins should be avoided. However, eradication of the cause, if possible, should be the best prevention for hypercalcaemia.

Prognosis

Prognosis in hypercalcemia resulting from causes other than malignancy is good, if treated on time and adequately with appropriate therapy. For hypercalcemia of malignancy, the decision to treat aggressively or not at will depend on the type of malignancy. In malignancy with one or more years of survival, hypercalcemia should be treated aggressively to reduce morbidity and improve survival. In malignancy with widespread metastasis and limited survival, a compassionate decision may be to withhold therapy for hypercalcemia.

Hypocalcemia

Hypocalcemia is defined as a serum calcium level <8.8 mg/dL in the presence of normal serum albumin. At a plasma pH of 7.4, each gram of albumin binds 0.8 mg/dL calcium. Clinical signs and symptoms of hypocalcemia are only observed if the ionized calcium concentration decreases (normally 4.5 to 5.5 mg/dL). Thus patients with decreased total serum calcium, which is often due to low albumin, may not have "true" hypocalcemia. In the clinical setting, reduced total serum calcium can result from a decrease in albumin secondary to liver disease, nephrotic syndrome, malnutrition, and other causes, such as protein-losing states. Alkalemia decreases ionized calcium whilst acidemia is protective. The common clinical settings in which hypocalcemia occurs are: acute and chronic renal failure, vitamin D deficiency, magnesium deficiency, acute pancreati hypoparathyroidism, acute and chronic respirat alkalosis, pseudohypoparathyroidism, infusion calcium-free albumin, phosphate or citrate infusion, a nutritional deficiencies. The clinical signs and sympto depend primarily on increased neuromuscular instabil secondary to a decrease in ionized calcium. Neurologi manifestations include mental instability, impair intellectual capacity, muscle cramps, tetany, depressi personality changes, and focal or generalized seizur Less common neurological signs include Parkinsonis hemiballism, choreoathetosis, dystonia, papilleder and oculogyric crisis. Signs of mental retardation m be present in children. Adults show dementia. T most important neuromuscular manifestations inclu muscle cramps, tetany, and paresthesia in the perio area and fingers and toes. Other organ systems may al be involved. Respiratory disturbances may develop fro laryngospasm and bronchospasm. In the cardiovascul system, hypocalcemia can affect the contraction cardiac muscle and result in prologation of the Q interval, arrhythmias, hypotension, and cardiac failur

Management of Hypocalcemia

The treatment of hypocalcemia depends on the caus severity, presence of symptoms, and rapidity of ons of symptoms. In symptomatic or severe hypocalcem associated with cardiac arrhythmias or tetany, calciu gluconate 10 percent (10 ml) administered intravenous over 20 minutes (1 ml/2 min) is recommended. symptoms persist, infusion of calcium is require Usually 10 to 15 mg of calcium per kg body weight or to 8 ampoules of 10 percent calcium gluconate is add to a liter of 5 percent dextrose in water and infus over a period of 4 to 6 hours. Serum calcium should monitored hourly to adjust infusion rates and maintai serum calcium between 7 and 8 mg/dL.

In asymptomatic hypocalcemia, oral therapy adequate. Low serum calcium associated with low seru albumin does not require calcium replacement. Calciu carbonate is an effective oral therapy. It is well tolerat and given in a dose of 1 g per os three times on an emp stomach. Calcium preparations given with meal w reduce serum phosphorus but will not increase seru calcium. Vitamin D supplementation in the form calcitriol (1, 25 $(OH)_2$ Vitamin D_3) in doses of 0.25 mg 0.5 mcg once daily will enhance calcium absorption fro the gut and kidneys and maintain serum calcium level at near normal or normal level. In magnesium deficiency associated with hypocalcemia as in malnutrition, magnesium supplementation will increase serum calcium. Magnesium can be given as magnesium oxide 400 mg per os three times daily. Higher doses can cause diarrhea. Patients with cardiac arrhythmias or on digoxin therapy need continuous ECG monitoring during calcium replacement therapy, because calcium potentiates digoxin toxicity. Prophylaxis with calcium and vitamin D therapy 24 to 48 hours prior to parathyroid surgery may prevent development of severe hypocalcemia following parathyroidectomy. In patients with hypoparathyroidism and pseudo-hypoparathyroidism, the hypercalcemic effect of thiazide diuretics may offer some additional benefits over and above calcium supplements. Since PTH deficiency impairs the conversion of vitamin D to calcitriol, the most efficacious treatment is calcitriol or 1-alphahydroxyvitamin D_3 in patients with severe hypoparathyroidism.

PHOSPHATE

Approximately 85 percent of body phosphorus is in bone as a part of the mineralized extracellular matrix. In addition, phosphorus plays a critical role in many metabolic processes within the cell; it is an integral component of the nuclei acid that comprise DNA and RNA. Phosphate bonds of ATP carry the energy required for all cellular functions. It is an integral component of phospholipid metabolism and functions as a buffer in bone, serum, and urine. The total plasma phosphorus concentration is approximately 14 mg/dL, of which approximately 4 mg/dL is in the inorganic form, which is measured. 80 to 85 percent of plasma phosphorus exists either as undissociated or "free" phosphate ions HPO_4^{2-} and H_2PO_4, and 10 to 15 percent is protein bound. Phosphate is predominantly an intracellular anion with a concentration of approximately 100 mmol/L. Hence phosphate entry into cells requires a facilitated transport process. Several sodium coupled transport proteins have been identified that enable intracellular uptake of phosphate by taking advantage of the steep extracellular-to-intracellular sodium gradient namely type 1, 2, and 3 transporters. As phosphate is a ubiquitous substance, it is plentiful in the diet. Intestinal absorption of phosphate is virtually unregulated with absorption occurring predominantly in the proximal small intestine. A normal diet contains about 1000 mg of phosphate of which two thirds is absorbed. Absorption is increased in the presence of vitamin D and a very low-phosphate diet. Absorption of phosphate is blocked by aluminium, calcium, and magnesium. About 100 to 300 mg/day of phosphate is lost in stool mainly as a result of sloughed intestinal cells and gastrointestinal secretions. Excess of ingested phosphate is excreted by the kidneys to maintain phosphate balance. Expansion of the extracellular fluid volume results in an increase and volume contraction in a decrease in urine excretion of phosphorus. The factors affecting renal phosphate excretion are shown in Table 2.

Apart from PTH and vitamin D, several other novel regulators of phosphate homeostasis have been identified through studies of serum factors associated with phosphate wasting syndromes, such as oncogenic osteomalacia and hereditary forms of hypophosphatemic rickets. The first to be discovered was a phosphate-regulating gene with homologies to endopeptidases on the X chromosome (PHEX). This is a neutral endopeptidase mutated in the syndrome of X-linked hypophosphatemic rickets. It is possible that PHEX might be responsible for the catabolism on a nonPTH circulating factor that regulates proximal tubule phosphate transport and vitamin D metabolism. When diagnosing disorders in phosphate metabolism, it is important to note that serum phosphate concentration varies with age, time of day, and fasting state. Serum phosphate concentration is higher in children than adults; the reference range is 4 to 7 mg/dL in children compared with 3 to 4.5 mg/dL in adults. A diurnal variation exists with the highest levels occurring near noon. The normal range of phosphate values are shown in Table 3.

Hyperphosphatemia

Hyperphosphatemia may occur because of 1 of 3 pathogenetic mechanisms:

- Excessive intake
- Decreased excretion
- Shift of phosphate from the intracellular to extra-cellular space.

Excessive Intake

In the presence of normal renal function, the serum phosphate levels can be maintained within normal range

Table 2. The factors affecting renal phosphorus excretion

Factor	*Excretion*	*Mechanism / Nephron Site*
Diet		
Volume expansion	↑	↑ Filtered load of P ↓ proximal and distal reabsorption
Phosphorus restriction	↓	↑ Proximal reabsorption
Metabolism		
Acidosis	↑	↓ Tubular reabsorption
Alkalosis	↓	↑ Tubular reabsorption
Hormones		
PTH	↑	↓ Proximal and distal reabsorption
Vitamin D (long term)	↑	↓ Proximal and distal reabsorption
Growth hormone	↓	↑ Proximal reabsorption ↑ GFR
Calcitonin	↑	↓ Tubular reabsorption
Thyroid hormone	↓	↑ Tubular reabsorption
Insulin	↓	↑ Proximal reabsorption
Phosphatonin	↑	↓ Proximal reabsorption
Diuretics		
Mannitol, loop diuretics, thiazides	↑	↑ Tubular reabsorption, site varies
Other		
Growth and Development	↓	↓ Proximal and distal reabsorption
Glucose	↑	Osmotic diuresis ↓ reabsorption proximal tubular
Glucocorticoids	↑	↑ Proximal reabsorption

↑ = increased: ↓ = decreased; GFR = glomerular filtration rate; PCT = proximal convoluted tubular; Pi = inorganic phosphat
Adapted with permission from Avner ED, Harmon WE, Niaudet P., eds. Disorders of Phosphorus, Calcium and Vitamin
Pediatric Nephrology (Philadelphia: Blackwell, 2004: 237-54).

Table 3. Normal and mean ranges of phosphate at different age

Age	*Range (mg/dL)*	*Mean (mg/dL)*
Neonate	4.8 - 8.2	6.8
Infants	4.8 – 7.4	6.2
1 – 2 years	4.5 – 5.8	5.0
2 – 13 years	3.5 – 5.5	4.4
Late adolescent - adults	2.7 – 4.7	3.4

despite unlimited quantities of phosphate ingestion. Most often, hyperphosphatemia is caused by a relative high intake of phosphate in the setting of impaired mechanisms for renal phosphate excretion (e.g., renal failure, milk-alkali syndrome).

Vitamin D intoxication can produce hyperphosphatemia as a result of excessive gastrointestinal absorption and increased renal reabsorption. Short-term administration of large quantities of phospha parenterally can produce hyperphosphatemia in patient with impaired renal function.

Fibroblast Growth Factor-23 (FGF-23)

Fibroblast growth factor-23 (FGF-23) is a newly discover phosphaturic hormone that has been found to be a k regulator of phosphate and vitamin D metabolism. It produced by osteoblasts and osteoclasts in mineral bo and requires the Klotho protein as a 'second messenge Klotho protein binds to multiple FGF receptors a increases their affinity to FGF-23, thereby regulati FGF-23 signaling. Klotho is expressed primarily in t renal tubules and the choroid plexus of the brain. T phosphaturic action of FGF-23 is mediated by reduci the number of electrogenic phosphate cotransporte and the electroneutral contransporters on the bru border membrane of the proximal tubulses. It al suppresses the action of 1-alpha hydroxylase, thereby decreasing synthesis of 1,25 $(OH)_2$ vitamin D and increase the action of 24-hydroxylase that increases hydrolysis of 1,25$(OH)_2$ vitamin D which is the inactive form of vitamin D. The reduction in the levels of 1,25$(OH)_2$ vitamin D levels leads to reduced absorption of phosphate from the intestine and thus reduction of serum phosphate levels. FGF-23 levels are increased in chronic kidney disease even before there are changes in serum calcium, phosphate or PTH levels. Levels of FGF-23 are positively correlated to levels of serum phosphate and PTH but have a negative correlation to 1,25$(OH)_2$ vitamin D levels and estimated glomerular filtration rate as well as tubular phosphate re-absorption. Recently higher levels of FGF-23 have been found to be associated with increased risk of deterioration of kidney function and episodes of rejection in recipients of kidney transplants in children. Thus in the future FGF-23 might prove to be a promising new therapeutic target for prevention of metabolic bone disease in patients with chronic kidney disease.

Decreased Excretion

Decreased excretion of phosphate, especially when coupled with excessive intake, is by far the most common cause of hyperphosphatemia. The commonest cause is acute or chronic renal failure. Hyperparathyroidism causes hyperphosphatemia through a failure to inhibit renal proximal tubule phosphate reabsorption. Syndromes of tubular resistance to PTH, including pseudohypoparathyroidism (1 a, 1 b, 1 c, and 2) and severe hypomagnesemia, which impairs PTH secretion and causes PTH resistance, manifest as hyperphosphatemia. Vitamin D intoxication also decreases loss of phosphate ions by the kidneys, thus enhancing the hyperphosphatemic effect.

Shift from Intracellular to Extracellular Space

The clinical situations in which this mechanism is the major cause of hyperphosphatemia includes rhabdomyolysis and tumor lysis syndrome. Rarely extracellular shifts of phosphate occur with insulin deficiency or acute metabolic acidosis.

The short-term complications of hyperphosphatemia include acute hypocalcemia with possible tetany and rarely acute deposition of calcium/phosphate complexes into joints, subcutaneous tissue, or other soft tissue. The long-term complications of chronic hyperphosphatemia can affect any organ system. However, the organs most commonly involved include the vascular system, bones, skin, joints, and heart.

Management of Hyperphosphatemia

If a possible cause for the hyperphosphatemia is found, treatment should be directed to the primary pathology. The most important clinical condition requiring decrease in phosphate intake is renal failure. It is important to avoid foods high in phosphate content, such as dairy products, nuts, meat, and other high-protein foods. In patients with advanced renal failure, dietary restriction alone may not be sufficient to control serum phosphate levels. These patients will require phosphate binders to inhibit gastrointestinal absorption of phosphate. Phosphate binders are taken concomitantly with meals and work by directly interacting with the phosphate in the food, preventing intestinal absorption.

Phosphate binders have become a bonanza for pharmaceutical industries and investigators as well. Benefit of phosphate binders to reduce cardiovascular morbidity and mortality is questionable. Increased calcium x phosphate product in the pathogenesis of cardiovascular disorders is more of a secondary mechanism than a primary pathophysiologic process. High blood flow during dialysis is probably the most important factor for loss of vascular wall integrity and secondary deposition of calcium x phosphate product in diabetic and or hypertensive patients where vascular wall injury is significant and, thus, they are more vulnerable to calcium x phosphate product deposition.

Nevertheless, over the years, aluminum hydroxide was successfully used to maintain serum phosphorus at a near normal level and was considered safe. Now, its use is considered unsafe. Aluminum hydroxide gel (Amphojel®) was prescribed in a dose of 30 ml with each meal. Because of the probable toxic effects associated with aluminium absorption from long-term use, it is seldom prescribed. Features of aluminum toxicity include dementia, osteomalacia and fracture, and anemia. However, in intractable hyperphosphatemia, Amphojel® may be used. Risk of aluminum toxicity is unwarranted.

Calcium-containing phosphate binders, e.g. calcium carbonate and calcium acetate. The calcium carbonate is given as 1 to 2 g with each meal. Calcium acetate (Phoslo®) is available in 667 mg tablet; average dose is

2 tablets three times daily with meal. The disadvantage associated with the use of these agents is hypercalcemia. Large exogenous calcium loads may lead to soft tissue calcification in patients with end stage renal disease. Sevelamer (Renagel®), a polymeric phosphate binder, is available as oral preparation. This drug is not systematically absorbed. Pharmaceutical company claims that Renagel® reduces phosphorus more effectively does not increase calcium x phosphorus product and, therefore, reduce cardiovascular morbidity and mortality. The beneficial effects of sevelamer, as claimed by pharmaceutical companies, cannot be confirmed. Renagel® is available as 400 mg or 800 mg tablet, usual dosage is 2 x 400 mg 4 times daily. This phosphate binder is more expensive than other phosphate binders. Adverse events are common ranging from nausea, vomiting in 20 percent, pain ad lib 13.1 percent, arthralgia in 12.1 percent, pruritus 13.1, hypertension 10.1 percent, and headache 9.1.

Editor strongly feels that best treatment for dialysis patients is prevention of dialysis. Adequate and robust control of blood glucose with insulin and adequate control of hypertension are the means to prevent patients progressing to dialysis, thus avoiding use of any phosphate binders irrespective of their merits.

The most effective way to lower phosphate in patients with end stage renal disease is by dialysis and transplantation. Better control of hyperphosphatemia is also achieved through control of secondary hyperparathyroidism. The agents most frequently used for control of secondary hyperparathyroidism are vitamin D metabolites and, more recently, calcium-sensing receptor agonists. Calcitriol, oral or intravenous preparation, in a dose of 1 to 4 mcg is used with each dialysis treatment. Calcium-sensing receptor agonists, such as cinacalcet (Sensipar®), can be used in dosage of 30 to 90 mg daily. Cinacalcet effectively lowers intact PTH level.

In patients with normal renal function and hyperphosphatemia, volume repletion with normal saline infusion, coupled with forced diuresis using loop diuretics, is effective. The increased intravascular volume inhibits proximal renal tubular absorption of phosphate, thus promoting phosphaturia. Surgery may sometimes be required for removal of large calcium phosphate deposits occurring in patients with tumoral calcinosis or long-standing renal failure.

Hypophosphatemia

Hypophosphatemia is defined as a phosphate level of less than 2.5 mg/dL (0.8 mmol/L). The morbidity of hypophosphatemia is highly dependent on cause, and severity. Mild and transient hypophosphatemia is generally asymptomatic and is not accompanied by long-term complications. Acute severe hypophosphatemia can result in widespread organ dysfunction. Acute hypophosphatemia can lead to myopathy, rhabdomyolysis, and acute renal failure. Acute hypophosphatemia can lead to cardiomyopathy and acute congestive heart failure. Chronic hypophosphatemia presents as metabolic bone disease.

Although hypophosphatemia can present at any age, the effects of chronic hypophosphatemia resulting from genetic syndromes usually present in infancy and early childhood. Acquired hypophosphatemia usually manifests in late adolescence or adulthood, usually as a result of eating disorders. With aging, hypophosphatemia is often related to alcoholism, tumors, malabsorption, or vitamin D deficiency.

The three major pathogenetic mechanisms resulting in hypophosphatemia are: inadequate intake, increased excretion, and shift from the extracellular to intracellular space.

Inadequate Intake

Inadequate intake of phosphate is common among poor, chronically ill patients, African-Americans, and the oriental population who are often intolerant of dairy products. Intestinal malabsorption and vitamin D deficiency can also exacerbate hypophosphatemia in cases of poor dietary ingestion. Concomitant use of antacids containing calcium, magnesium, or aluminum causes hypophosphatemia by inhibiting intestinal absorption.

Increased Excretion

Since the kidneys play a pivotal role in phosphate homeostasis, it is not surprising that the most common mechanism for the development of hypophosphatemia is increased renal phosphate excretion secondary to hyperparathyroidism. Hypophosphatemia in this setting is usually mild. Increased phosphate excretion can also be induced by forced saline diuresis due to the inhibitory effects of saline diuresis on all proximal tubule transport processes. Vitamin D deficiency also contributes to hypophosphatemia by decreasing renal phosphate absorption.

Shift from Extracellular to Intracellular Space

The most common cause of hypophosphatemia in hospital setting is infusion of 5 percent dextrose in water without or with insulin. Other causes are treatment of diabetic ketoacidosis, refeeding, short-term increase in cellular demand (e.g., hungry bones syndrome), and metabolic alkalosis. Severe hypophosphatemia is common and mulitfactorial in alcoholic patients. In acute alcohol withdrawal or delirium tremens, increased plasma insulin and epinephrine along with acute respiratory alkalosis promote intracellular phosphate shift resulting in severe hypophosphatemia.

Clinical Presentation

Most patients with hypophosphatemia are not symptomatic. Symptoms of hypophosphatemia are often nonspecific and depend on cause, duration, and severity of hypophospatemia. Most often, symptoms are present in patients with severe and/or chronic hypophosphatemia. Patients with chronic phosphate-wasting syndromes frequently present with bone pain, muscle weakness, and skeletal disorders. Associated clinical findings include poor nutrition, symptoms of malabsorption, excessive antacid use, treatment with parental nutrition, heavy metal exposure, use of drugs, such as glucocorticoids, cisplatin, or pamidronate, intensive burns, and use of growth factors. Severe acute hypophosphatemia may present with disorientation, seizures, focal neurological findings, cardiac failure, and muscle pain.

Treatment

Medical care is dependent on the cause, severity, and duration of hypophosphatemia. In patients with malabsorption, specific therapy is directed at the underlying illness with the addition of vitamin D supplements. To normalize phosphate levels, oral phosphate supplements are used. Long-term therapy with oral supplements used in the treatment of genetic disorders of phosphate wasting can often normalize phosphate levels and decrease bone pain. Parenteral phosphate supplementation is prescribed for patients who have severe hypophosphatemia (serum phosphate ≤1 mg/dL) or nonfunctional gastrointestinal syndromes. Vitamin D therapy is used in patients with vitamin D deficiency. In severe hypophosphatemia (serum phosphorus equal to or less than 1 mg/dL), phosphorus can be administered as 30 mmol of sodium or potassium phosphate, if potassium is also low, in one-half normal or normal saline infusion at a rate of 30 to 50 ml/h x 6 hours. Serum phosphate should be monitored every 4 to 6 hours to adjust the rate. When serum phosphate is 2.8 to 3 mg/dL, intravenous therapy shall be discontinued, and oral therapy is initiated. In patients with renal failure, more caution must be exercised in giving intravenous phosphorus. Surgery is often indicated in patients with primary hyperparathyroidism. Patients with oncogenic osteomalacia are cured by excision of the tumor, thereby eliminating the cause of the phosphate wasting and relative vitamin D deficiency.

KEY POINTS

- Lung and breast cancers account for 60 percent of all cancers associated with hypercalcemia.
- Hypercalcemia is a rare complication of prostate cancer.
- Gastric and colorectal cancer are virtually never associated with hypercalcemia.
- Hypercalcemia associated with normal or elevated serum phosphorus level and with or without abnormal renal function is mostly caused by malignancy.
- Hypercalcemia associated with low-serum phosphorus, despite abnormal renal function, strongly suggests primary hyperparathyroidism.
- The triad of hypercalcemia, acute renal failure, and metabolic alkalosis suggests milk alkali syndrome.
- In elderly or critically ill patients, significant cognitive impairment may be seen even with mild hypercalcemia (≥12 mg/dL).
- In general, the higher the level of serum calcium, the more likely malignancy is the underlying cause of hypercalcemia.
- Good hydration is the vital preventive measure, because dehydration aggravates hypercalcemia.
- Osteoclastic bone reabsorption is the principal pathophysiologic alteration in severe hypercalcemia associated with hyperparathyroidism or malignancy.
- Hypercalcemia impairs renal excretion of sodium, which is a cotransporter for calcium, thereby further aggravating hypercalcemia. This is further worsened by volume depletion.

- PTH and PTHrP enhance further renal tubular reabsorption of calcium.
- Hydration with intravenous infusion of isotonic saline is the essential first step of treatment of hypercalcemia, regardless of the etiology.
- The cornerstone of therapy is inhibition of osteoclastic bone reabsorption by one of the inhibitors: calcitonin, a biphosphonate, plicamycin (mithramycin), and/or corticosteroids. A biphosphonate preparation, ADP or pamidronate 90-mg single intravenous infusion, is considered most effective. The action lasts longer than other agents and side effects are mild.
- Corticosteroids are effective in hypercalcemia caused by myeloma and lymphoproliferative disorders. Corticosteroids can be combined with calcitonin or a biphosphonate.
- The most important part of treatment of hypercalcemia is to identify and treat the cause so that recurrent hypercalcemia is prevented or minimized.

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11

Generalized Edema (Anasarca): A Systematic Approach to Diagnosis and Management

Anil K Mandal

ABSTRACT

Edema is defined by fluid accumulation in the tissues and its onset frequently is first noticed by the patients. Mild edema is common and reversible. Generalized edema requires intensive therapy. Causes of edema are numerous. Investigation of the causes is essential for appropriate therapy.

ANATOMY AND PHYSIOLOGY OF EDEMA

Edema is defined as the presence of excessive amount of fluid in the tissues of the body. Fluid accumulates mainly in the extracellular fluid compartment (ECFC), but it can also accumulate in the intracellular fluid compartment (ICFC). ECFC consists of intravascular fluid space and interstitial fluid space. Sixty percent of total body weight is body water; two thirds of which reside in ICFC, and one third in the ECFC. For the total amount of fluid in the ECFC, 40 percent is in the intravascular space as blood or plasma and 60 percent in the interstitial space. Fluid is filtered from intravascular space into the interstitial space at the arteriolar end of a capillary by high pressure and then diffuse back into the intravascular space at the venous end of the capillary. This is a continuous process and affected mainly by the difference in hydrostatic pressure in the venous end of the capillary, and the oncotic pressure exerted by plasma albumin. Under normal condition, fluid does not accumulate in the interstitial space as interstitial fluid pressure is negative (-17 mmHg), hence no edema is detectable. As fluid continues to accumulate in the interstitial space and interstitial fluid volume increases, interstitial fluid pressure increases in parallel with the volume, when edema becomes detectable. Lymph flow can increase as much as 10-fold to 50-fold. The lymph vessels can carry away large amounts of fluid as they are formed and help to prevent the interstitial fluid pressure from rising into the positive pressure range. As the lymph flow increases, it carries away protein from the interstitium, thus reducing the interstitial fluid colloid osmotic pressure. This is called "washdown" of the interstitial fluid protein. As washdown occurs, the differential gradient between plasma colloid osmotic pressure and the colloid osmotic pressure in the interstitium increases, thus increasing the osmotic absorption of fluid from the interstitium into the capillaries. The reverse will occur with reduced plasma colloid osmotic pressure, allowing stagnation of fluid into the interstitium.

Therefore, excessive fluid accumulation in the interstitial space initially may occur in one of the following two ways:

1. Abnormal leakage of fluid from the blood capillaries, or
2. Reduced plasma oncotic pressure due to low plasma albumin.

Abnormal leakage of fluid from the capillaries may occur in congestive heart failure (CHF), acute glomerulonephritis, angioedema, and venous obstruction, e.g., inferior vena cava obstruction due to thrombosis or from extrinsic compression by a tumor or subclavian vein stenosis caused by a catheter placement for temporary access to hemodialysis. Low serum albumin as in cirrhotics or nephrotics reduces the oncotic pressure gradient and hinders return of filtered plasma water at the venous end. Once fluid begins to accumulate in the interstitial space, further accumulation of fluid occurs mainly through renal retention of sodium and water. The main stimulus for renal retention of sodium and water is decreased effective arterial volume (EABV), which causes activation of two major hormones, namely aldosterone and vasopressin. By acting on the kidney, they cause sodium and water retention and result in sustained edema. The renal mechanism in the participation of sustained edema is presented in Figure 1.

ETIOLOGIES OF EDEMA

Causes of edema can be divided into the following groups:

A. Edema associated with significant proteinuria (>0.5 g/24h)
   - Renal disease
   - Unilateral or bilateral renal vein thrombosis
   - Preeclampsia

B. Edema associated with slight or no proteinuria (<0.5 g/24h)
   - CHF
   - Cirrhosis of liver
   - Malnutrition
   - Inferior vena cava thrombosis below the renal veins
   - Hypothyroidism
   - Varicose veins

C. Causes of generalized edema (Anasarca)
   - Nephrotic syndrome
   - CHF
   - Cirrhosis of liver
   - Malnutrition
   - Microcystic disease of newborn

D. Generalized edema associated with orthopnea, paroxysmal nocturnal dyspnea, distended neck veins, hepatomegaly, pleural effusion
   - CHF

E. Generalized edema associated with ascites
   - Cirrhosis of liver
   - Pelvic malignancy with spread into peritoneum, inferior vena cava, superior vena cava. Examples: Lymphoma, Metastasis
   - Lymphedema due to lymphatic obstruction by tumor, parasite (filarial). In the letter case, ascites is chylous.

F. Edema associated with drug therapy

Two groups of drugs are mainly incriminated to cause edema: (1) Antihypertensive drugs, and (2) Antihyperglycemic therapy. Vasodilator drugs, including hydralazine, dihydropyridine calcium channel blockers (CCB), minoxidil or pentoxifylline are likely to cause edema. The exact mechanism of edema due to vasodilation has not been elucidated. However, increased capillary permeability has been postulated. Complaint of edema is common among patients treated with amlodipine (Norvasc®), a CCB. Minoxidil also causes pleuropericardial effusion. With regard to antihyperglycemic therapy, insulin, and thiazolidinedione (TZD) groups of oral antidiabetic agents have been reported to cause edema. Two recent review articles document edematogenic properties of insulin. Insulin treatment has been associated with weight gain, mild-to-moderate edema, and rarely generalized edema and cardiopulmonary congestion. Weight gain is a common feature of insulin therapy; however, insulin-related weight gain may occur with no detectable edema. The mechanism of weight gain

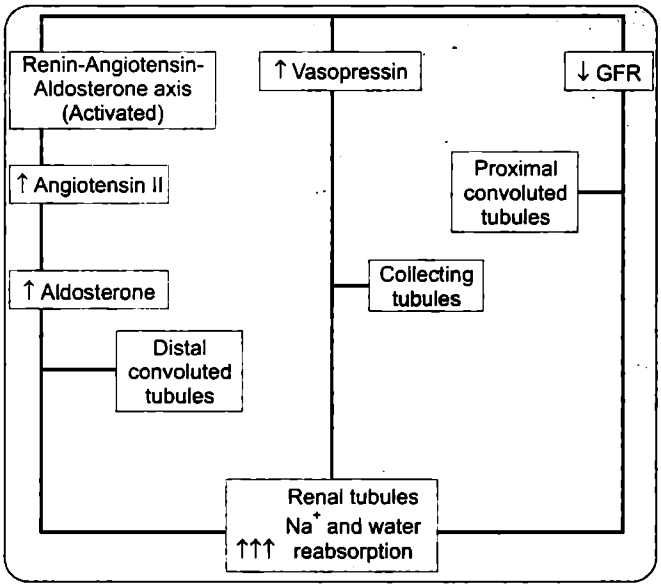
Renin-Angiotensin-Aldosterone axis (Activated)
↑ Vasopressin
↓ GFR
↑ Angiotensin II
Proximal convoluted tubules
↑ Aldosterone
Collecting tubules
Distal convoluted tubules
Renal tubules Na⁺ and water ↑↑↑ reabsorption

Figure 1: Effective circulating blood volume (ECBV). If ECBV is diminished, there is increased production of renin-angiotensin and aldosterone, which promotes excessive sodium reabsorption in the distal convoluted and collecting tubules. As a result of decreased GFR, proximal tubular Na^+ reabsorption is enhanced. Aldosterone enhances distal tubular Na^+ reabsorption, whereas vasopressin enhances water reabsorption in the collecting tubules

has not been defined, but fat accumulation and fluid retention are likely to be involved. Insulin also has an antinatriuretic effect, but tubular site of action of insulin in promoting sodium reabsorption has not been clarified. Ascending thick limb of Henle's loop and distal tubule have the greatest density of insulin receptors. In addition, insulin stimulates Na^+, K^+ adenosine triphosphatase (ATPase), a cation transport system abundant in distal tubules.

Regardless of the mechanism, insulin edema responds well to diuretics, suggesting sodium retention as the principal mechanism of insulin edema. Weight gain is more common and severe with use of NPH insulin than insulin glargine (Lantus®). Clinically, insulin edema may present from mild pedal edema to frank anasarca. In volume-depleted, malnourished diabetes patients, increased insulin requirements may reduce the renal excretion of sodium and increase free water retention, resulting in edema.

Among the TZD, two products are used in the United States. These are pioglitazone (Actos®) and rosiglitazone (Avandia®). A common side effect is weight gain and fluid retention, which could lead to CHF. In a premarketing clinical trial of TZDs, a new onset or exacerbation of CHF occurred at a cumulative rate of 3.5 percent for patients administered a TZD plus insulin.

A recent study has shown that hydrochlorothiazide (HCTZ), spironolactone, or amiloride prevents TZD-induced increase in body weight. There was no significant difference between HCTZ and spironolactone. These findings are consistent with peroxisome proliferator-activated receptor-γ (gamma) activation of the epithelial sodium channel in the distal collecting tubule, a site of action of spironolactone and a potential target for thiazide diuretics.

IDIOPATHIC EDEMA

Idiopathic edema is commonly seen in menstruating females. In some females, prolonged upright position may be a cause; while in others, diuretic abuse may be a primary factor in initiating edema. Females abuse diuretics to lose weight. Chronic diuretic use leads to secondary hyperaldosteronism with sustained sodium retention and worsening of ankle swelling for as long as two weeks after cessation of diuretics. In some females, since edema develops with the onset of menstruation, relationship with estrogen is postulated.

SIGNS, SYMPTOMS, AND LABORATORY TESTING

Renal Disease Edema

Percutaneous renal biopsy study is the surest way t establish a diagnosis of renal disease. However, history physical findings, and renal function testing can ai to indirectly assess the type of renal disease in a given patient. Degree of proteinuria helps to differentiate between glomerular and tubulointerstitial disease Twenty-four hours proteinuria of more than 3g i consistent with primary glomerular diseases. Twenty four hours proteinuria of less than 3g is common in secondary glomerular diseases, which include diabetic nephropathy, lupus nephritis, vasculitis (for example Wegener's granulomatosis, polyarteritis nodosa) Twenty-four hours proteinuria less than 1g is common in acute and chronic tubulointerstitial renal disease and hypertensive renal disease (essential hypertension). **It should be noted, however, that severity of proteinuria does not distinguish one renal disease from another.**

Heavy proteinuria greater than 3g per 24 hours (nephrotic syndrome) may occur in malignant hypertension, renovascular hypertension, scleroderma, toxemia of pregnancy, and diabetic nephropathy. Thus, heavy proteinuria cannot distinguish preeclampsia from primary renal diseases. Therefore, in a given patient, heavy proteinuria, with anasarca, normal or near normal renal function (serum creatinine <1.4 mg/dL or eGFR* >60 ml/min) but without hypertension or mild hypertension and absence of retinopathy, suggests minimal lesion disease. In another patient, who has heavy proteinuria, moderate-to-severe hypertension, and mild-to-moderate impairment of renal function (serum creatinine ≥2 mg/dL), the likely diagnosis is membranous glomerulonephritis (GN), membranoproliferative GN, or focal glomerular sclerosis. The features just described in association with exudative retinopathy suggest diabetic nephropathy, while those in association with cardiomegaly and or glossomegaly suggest amyloidosis.

Common causes of nephrotic syndrome are (nephrotic syndrome by definition is proteinuria of ≥3.5 g/24h and accompanied by hypoalbuminemia and hyperlipidemia):

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*eGFR = estimated glomerular filtration rate (MDRD).

1. Minimal lesion disease
2. Membranous GN
3. Membranoproliferative GN
4. Focal glomerular sclerosis
5. Diabetic nephropathy
6. Amyloidosis

Congestive Heart Failure

Common features of CHF are persistent and moderate-to-severe shortness of breath along with edema of the lower extremities, ascites, and unilateral or bilateral pleural effusion. Other findings include inability to lie flat in bed and sitting up on the bed or propped up in bed to catch breath, distended neck veins, gallop rhythm in heart auscultation, and diminished air entry with rales at the lung bases. Recommended investigations comprise a chest X-ray, an echocardiogram, and MUGA scan. [MUGA = Multigated Acquisition (equivalent to Equilibrium Radionuclide Angiocardiography)]. Chest X-ray reveals extent of cardiomegaly, severity of pulmonary congestion, and presence of usually bilateral pleural effusion. A chest X-ray can determine the extent of the effusion and the need for thoracentesis.

Echocardiogram and MUGA scan will provide estimate for ventricular function and left ventricular ejection fraction. The lower the ejection fraction, the more severe is the impairment of renal function and more marked is the retention of sodium and water. In the presence of severely impaired renal function, edema and pulmonary congestion are likely to worsen and become progressively resistant to any form of medical treatment.

Cirrhosis of Liver

Hypoalbuminemia causing decreased effective circulating volume is perhaps the most important stimulation for avid renal sodium retention in cirrhosis. Elevated circulating aldosterone and vasopressin levels, by enhancing distal Na^+ and water reabsorption further aggravate edema and ascites.

Acute Glomerulonephritis Associated Beta Hemolytic Streptococcal Infection

This is a common illness in children but very uncommon nowadays due to prevention of this infection by penicillin. Children are typically brought into a doctor's office by the parents who notice puffiness of the face and dark-colored urine. The children usually have mild-to-moderate proteinuria, high ASO titer, positive throat culture, and low serum complement levels. They can be hypertensive, which is mostly volume dependent and responsive to treatment with a loop diuretic. This is a self-limited disease and long-term complications are rare. Recurrence can be prevented by long-acting penicillin (Bicillin®) or erythromycin (if allergic to penicillin).

Acute GN also can be caused by a variety of infection, such as pneumococcus bacteria or viruses. Among the viruses, parvovirus infection has been reported to cause generalized edema in adults.

Lymphedema

Lymphedema can be primary or secondary. Primary forms of lymphedema have a female predilection. Primary form of lymphedema is due to reduction in size and number of lymphatic vessels. Secondary lymphedema is most commonly seen mainly in two settings: (1) in breast cancer with lymph node resection or irradiation of the breast; (2) as a result of an elevated venous hydrostatic pressure, such as subclavian vein stenosis. High output lymphatic failure is seen in patients with cirrhosis, nephrotic syndrome, right-sided heart failure, and venous insufficiency.

Lipedema

Lipedema is different from lymphedema. Lipedema is a lipodystrophy, but the pathogenesis is poorly understood. Morphologically, there is an increase in both size and number of adipose tissue cells that result in symmetrical enlargement of the thighs, legs, and buttocks, while sparing the feet. The edema appears to progress over time and is believed to be due to lymphatic insufficiency. The lymphatic system is structurally normal, however.

Other Causes of Edema

Beriberi, a condition due to thiamine deficiency, leads to peripheral edema. An underlying mechanism is arteriolar vasodilation, which causes sodium retention. Angioedema and urticaria are not uncommon, and they occur as a result of hypersensitivity reaction to a host of drugs, chemicals, and bee estings. Among the drugs, the notable ones are antibiotics and angiotensin converting enzyme (ACE) inhibitor drugs.

ASSESSMENT OF EDEMA

Diagnosis of edema is essentially a clinical one. Laboratory and radiological investigations are required to establish its cause so that appropriate therapy can be prescribed. Weight gain due to expansion of the extracellular fluid volume usually precedes the onset of the peripheral edema. The causes of edema can generally be defined by the onset (acute or chronic), localized or generalized, accompanying symptoms, such as shortness of breath, paroxysmal nocturnal dyspnea, and tissue characteristics, such as skin pigmentation or thickening of skin, as in myxedema.

Unilateral lower extremity edema is most commonly due to deep venous thrombosis involving popliteal or femoral vein or pelvic venous system. Recurrent unilateral lower extremity edema could be due to extrinsic compression of iliac veins by a malignant process. Similarly, unilateral upper extremity edema is almost invariably due to venous thrombosis from prolonged intravenous fluid administration, hyperalimentation, antibiotic therapy, or occlusion of subclavian venous system caused by tunnel catheter placement or arteriovenous fistula for hemodialysis.

Generalized edema associated with ascites and pleural effusion is due to systemic diseases, such as acute or chronic kidney diseases (already stated), CHF, cirrhosis of liver, and severe protein malnutrition. Bilateral lower extremity massive edema without edema of the upper extremities, ascites, or pleural effusion is due to inferior vena cava obstruction. In males, left testicular swelling in the presence of anasarca indicates left renal vein thrombosis (left testicular vein drains into left renal vein). This may be seen in membranous or membranoproliferative glomerulonephritis or renal cell carcinoma of the left kidney.

Laboratory and Radiologic Investigations

Routine laboratory investigations consist of blood count, urinalysis, renal function panel, thyroid function test with thyroid-stimulating hormone (TSH), an electrocardiogram, and a chest X-ray. A large heart, pulmonary congestion, or bilateral pleural effusion indicates CHF. An arterial blood gas showing low oxygen and high PCO_2 is a supportive evidence of CHF.

Venous Doppler of the lower extremity, unilateral or bilateral for deep venous thrombosis, is essential. CT scan of the abdomen and pelvis is indicated when inferior vena obstruction is a consideration. Contrast enhancement is avoided when renal function is impaired. Magnetic resonance imaging (MRI) of inferior vena cava and renal veins is useful, when renal function is normal, but its use is limited nowadays because of the risk of gadolinium-induced nephrogenic sclerosing fibrosis. The risk is low when renal function is normal. The risk is high when renal function is impaired and much higher when patient is on hemodialysis. Echocardiogram is a commonly used technique to determine left ventricular function and ejection fraction. MUGA scan or equilibrium radionuclide angiocardiography is another technique for assessment of ejection fraction.

Lymphoscintigraphy evaluates the functional integrity and architecture of the lymphatic vessels. This imaging study is considered to be the test of choice in assessing chronic edema thought to be of lymphatic origin. Radiocontrast lymphography is reserved for cases of indeterminate interpretation on lymphoscintigraphy or in patients in whom surgery is considered for lymphedema. However, the limitation of radiocontrast use applies as in radiocontrast venography or CT scan.

THERAPEUTIC OPTIONS

1. Bed rest
2. Variable restriction of salt and water
3. Diuretic therapy
4. Diuretic infusion
5. Ultrafiltration via dialysis method
6. Treatment of the cause

Bed Rest

Bed rest alone helps to mobilize fluid from the dependent portions of the body and results in mild diuresis. Supportive stockings add further to the mobilization of fluid. The mechanism of diuresis induced by bed rest and/or supportive stockings is not clearly understood but appears to be due to increase in effective arterial blood volume and renal perfusion.

Since both dependency and limb immobility contribute to edema, patients are encouraged to exercise the limb. Leg elevation is not as effective in lymphedema as it is in venous edema, because higher external compression pressures are needed to transport fluid in lymphedema. Since venous insufficiency may be associated with lymphedema, exercise in the form of walking or stationary bicycling with a compression garment may be helpful in the mobilization of fluid. However, these maneuvers are not helpful when edema is due to systemic disorders or hypoalbuminemia.

Variable Restriction of Salt and Fluid Intake

Unless salt and fluid intake is restricted, sodium and water balance will remain positive. Salt intake can be determined by sodium excretion rate. One 24-hour urinary sample should be obtained for sodium excretion after 2 gram and 4 gram sodium intake for three days each, respectively. These urinary collections should be obtained in the absence of diuretic use. (Urinary electrolytes are not adequately interpretable if urinary samples are collected during diuretic therapy.) If a 24-hour urinary sodium excretion is less than 20 mEq/L on 2-gram or 4-gram daily sodium intake, then daily sodium intake should be reduced to 1 gram (23 mEq) or 0.5 gram, which is essentially a salt-free diet. Such hardship in salt intake is not generally necessary with the availability of a variety of potent diuretics. However, some patients develop resistance to diuretic therapy, and restriction of salt and fluid intake remains as the mainstay of therapy.

For reason of inability to excrete free water and the concomitant hyponatremia observed in patients with anasarca, free water intake should be equal to or less than daily urine output plus insensible loss (500 to 1000 ml/day, depending on living conditions) plus any additional loss.

Diuretic Therapy

There are three classes of diuretic that are commonly used. These are:

1. Thiazide diuretics
2. Loop-acting diuretics
3. Potassium-sparing diuretics

Acetazolamide is an inhibitor of proximal tubule bicarbonate reabsorption and, therefore, not classified as a diuretic.

Thiazide Diuretics

Actions:

1. Attributable solely to inhibition of sodium and chloride reabsorption in the distal convoluted tubule.
2. Act independent of carbonic anhydrase inhibition.
3. Partially decrease free water clearance or partially decrease ability to maximally dilute urine.
4. Do not interfere with the ability to concentrate urine in the face of hydropenia.

Thiazide diuretics induce natriuresis to the extent of 5 to 7 percent of filtered sodium and, therefore, considered relatively mild diuretics. A thiazide diuretic alone may be adequate in cirrhotics but prove to be ineffective in CHF or nephrotic patients.

All thiazide diuretics are sulfonamide derivatives and include:

1. HCTZ: available as 25, 50, or 100 mg tablets alone or in combination with potassium-sparing agents.
2. Indapamide (Lozol®): available as 2.5 mg tablet.
3. Metolazone (Zaroxolyn®): available as 0.5, 2.5, or 10 mg tablets.

Recommended dosage: HCTZ 12.5 to 25 mg twice daily; indapamide 2.5 to 5 mg once daily in the morning; metolazone 2.5 to 10 mg once daily in the morning. A common combination product is HCTZ with triamterene 25/37.5 mg (Dyazide® or Maxzide®).

Loop-acting Diuretics

A. Sulfonamide derivatives:
   1. Furosemide (Lasix®)
   2. Bumetanide (Bumex®)
   3. Torsemide (Demadex®)
B. Phenoxyacetic acid derivative: Ethacrynic acid (Edecrin®)

Furosemide is available as 20, 40, and 80 mg tablets. Bumetanide is available as 0.5, 1, and 2 mg tablets. Ethacrynic acid is available as 25 and 50 mg tablets.

Mode of Actions

1. Hemodynamic
2. Tubular

Hemodynamically, loop-acting diuretics have shown to increase renal blood flow and, in some instances, glomerular infiltration rate. These effects appear to be mediated by prostaglandins (PGs), since the natriuretic and diuretic effects are blunted by the use of prostaglandin synthesis inhibitors, such as indomethacin. In the renal tubules, loop-acting diuretics act on the ascending thick limb of loop of Henle and inhibit 2 chloride and 1 sodium transport, amounting to excretion of 15 to 20 percent of filtered sodium and chloride. Therefore, the natriuresis and diuresis can be quite marked. One bolus of intravenous injection of furosemide of 40 mg in an individual with normal renal function could result in diuresis of 5 to 6 liters in a matter of a few hours.

Thus, loop diuretics are very potent diuretics and, by inhibiting sodium chloride transport in the ascending thick limb, impair formation of hypertonic medullary interstitium. Hypertonicity in the medullary interstitium generates the gradient for final concentration of urine under the influence of arginine vasopressin. Therefore, a patient who is treated with a loop diuretic will be unable to maximally concentrate the urine during hydropenia. Loop diuretics also markedly reduce diluting capacity during water diuresis.

Dosage and Administration

The most commonly used loop diuretic is furosemide, and oral administration is the most common form of treatment. Recommended dosage regimen is 40 mg per oral twice daily in nephrotic syndrome or CHF, while 40 mg once daily in cirrhosis of liver.

Equivalent dosages of bumetanide and ethacrynic acid are 0.5 mg and 25 mg twice daily, respectively. In acute CHF with pulmonary edema, an intravenous bolus of furosemide 40 mg two to three times daily produces a dramatic result with prompt relief of shortness of breath. Intravenous bolus of a loop diuretic reduces left ventricular filling pressure and pulmonary edema and, consequently, shortness of breath. Intravenous administration of a loop diuretic does not always produce a dramatic effect in chronic CHF, as it does in acute CHF. Relief of pulmonary edema, which is noted with intravenous furosemide therapy, is not observed with oral furosemide therapy. It should be noted that, in the event an intravenous loop diuretic is a recommended therapy, furosemide or torsemide is safer than ethacrynic acid due to high risk of ototoxicity of the latter. If the expected effect is not observed with commonly used furosemide, it is desirable to try torsemide. However, in case of allergy to sulfa drugs, the only safe loop diuretic that can be used is ethacrynic acid. Furosemide has been reported to cause severe allergic reactions, including exfoliative dermatitis, and acute allergic interstitial nephritis with acute renal failure. Therefore, furosemide, bumetanide, should be stopped if skin rash or dermatitis occurs and kidney function is rapidly decreased.

Adverse Effects of Thiazide and Loop-acting Diuretics

The adverse effects of thiazide and loop-acting diuretics are similar and relate to fluid, electrolyte, metabolic, and acid-base disturbances. The electrolyte disturbances include hyponatremia, hypochloremia, hypokalemia and hypomagnesemia. Renal insufficiency with elevated BUN/serum creatinine ratio, which is suggestive of volume depletion, is a common complication of diuretic therapy. A simple metabolic alkalosis is a concomitant accompaniment of electrolyte disturbances. The two common metabolic disturbances are hyperglycemia and hyperlipidemia. Hyperglycemia relates to hypokalemia or dehydration, either of which blunts insulin release and gives rise to hyperglycemia (see later). The relationship of hyperglycemia with dehydration may be more important than with hypokalemia, since saline infusion generally corrects hyperglycemia, whereas increasing serum potassium level with potassium supplements does not always correct hyperglycemia. Hyperlipidemia, mostly elevated serum cholesterol, is very common with diuretic therapy. However, elevation of cholesterol wears off in chronic diuretic users. Although cardiovascular risk of hyperlipidemia with diuretic therapy is stressed, it has not been substantiated. In most all cases, the adverse effects, including hyperglycemia and hyperlipidemia caused by diuretic therapy, reverse upon discontinuation of diuretic therapy. These will be exemplified here.

Case Scenario No. 1

A 69-year-white male had a regular visit to hypertension clinic on July 7, 1993, for follow-up treatment of hypertension. He was receiving Maxzide• 25 (hydrochlorothiazide 25 mg + triamterene 37.5 mg) one tablet daily and nifedipine 10 mg three times daily per oral. A laboratory study was done on the day of the visit. Based on the results, Maxzide• was discontinued, and laboratory study was repeated two weeks later. The laboratory results are presented in Table 1. From Table 1, it should be noted that the patient had hyperglycemia and renal insufficiency. Two weeks after discontinuation of diuretic therapy, blood glucose returned to normal level and renal function improved. The latter changes are likely to be due to volume repletion, which is evident by the increase in urinary sodium concentration and the slight decrease in urinary creatinine concentration.

Case Scenario No. 2

A 72-year-white male had a routine follow-up visit to hypertension clinic. He has a history of CHF. He was receiving furosemide 40 mg per oral twice daily. During a visit on August 13, 1993, furosemide dose was increased to 60 mg BID and metolazone 2.5 mg was added to the regimen. Blood samples were drawn on May 12, August 13, and August 23, 1993. The results are presented in Table 2. From Table 2, it should be noted that the patient had progressive loss of weight and increase of hemoglobin and hematocrit and progressively severe hypokalemia, hypochloremia, metabolic alkalosis, and renal insufficiency. The increases in hemoglobin and hematocrit are due to hemoconcentration, which is the result of volume depletion. However, despite hypokalemia and dehydration, his blood glucose did not increase. Uric acid and cholesterol levels were elevated. Loop diuretic therapy is probably the most common cause of hypochloremic hypokalemic metabolic alkalosis nowadays. In most cases, patients are asymptomatic or mildly symptomatic and generally require no aggressive treatment except adjustment of the dose or discontinuation of diuretic therapy.

Table 1. 69 y WM: adverse effects of diuretic therapy

1993	July 07	July 21
Serum Values (Fasting)		
Glucose (mg/dL)	200	105
BUN (mg/dL)	30	19
Creatinine (mg/dL)	2.1	1.7
Sodium (mmol/L)	140	143
Potassium (mmol/L)	3.7	3.9
Chloride (mmol/L)	104	107
CO_2 (mmol/L)	26	28
Urinary Values (Spot Urine)		
Sodium (mmol/L)	37.4	86.5
Creatinine (mg/dL)	165	149.4

Table 2. 72 y WM: adverse effects of diuretic therapy

Parameters	May 12, 1993	August 13, 1993	August 23, 1993
Furosemide	40 mg PO BID	40 mg PO BID	60 mg PO BID
Metolazone	No	No	2.5 mg PO daily
Weight (lbs)	191	187	180
BP sitting (mmHg)	122/63	125/68	129/76
Hemoglobin (g/dL)	11.9	13.2	14.5
Hematocrit (%)	36.3	40.5	43.5
BUN (mg/dL)	37	35	67
Serum creatinine (mg/dL)	1.6	1.5	1.8
Serum Na^+ (mmol/L)	139	139	141
Serum K^+ (mmol/L)	4.0	3.8	3.0
Serum Cl^- (mmol/L)	104	99	88
Serum CO_2 (mmol/L)	29	32	39
Serum glucose (mg/dL)	92	ND	89
Serum uric acid (mg/dL)	8.4	ND	13.2
Serum cholesterol (mg/dL)	151	ND	200

PO = per os (by mouth); ND = not done; BID = twice daily.

Case Scenario No. 3

A 60-year-white male was a hypertension clinic follow-up patient. His diagnoses include alcoholic cirrhosis, acute and chronic CHF, and chronic atrial fibrillation. Physical examination revealed slight shortness of breath and bilateral lower extremity edema. Furosemide was substituted by bumetanide. The results of his arterial blood gas studies and other laboratory studies are presented in Table 3.

Table 3 demonstrates that patient had hyponatremia, hypochloremia, hypokalemia, and associated simple metabolic alkalosis. The markedly elevated BUN/serum creatinine ratio (44, n=20) strongly suggests severe volume depletion, which along with hypochloremia and hypokalemia resulted in metabolic alkalosis (pH = 7.51).

Diuretic therapy, especially loop diuretic, can reduce renal function to a great extent in patient with chronic renal failure mainly due to volume depletion. Reduction of the dose of the diuretic often promptly improves renal function to baseline levels. For example, a patient with chronic renal failure was treated with 40 mg per oral furosemide daily. His serum creatinine as of October 6, 1993, was 5.9 mg/dL. Furosemide was reduced to 20 mg

Table 3. 60 y WM: adverse effects of diuretic therapy

Serum Values		Blood Gas Analysis	Normal Range
Glucose (mg/dL)	114		
BUN (mg/dL)	44	pH 7.51	7.35–7.45
Creatinine (mg/dL)	1.0	PCO_2 46.7	34–45
Sodium (mmol/L)	132	PO_2 72	75–108
Potassium (mmol/L)	2.9	Bicarbonate 38	18–23
Chloride (mmol/L)	83		
CO_2 (mmol/L)	36.8		

daily. Three weeks later, his serum creatinine decreased from 5.9 to 5.4 mg/dL. During the same period, his serum glucose decreased from 150 to 127 mg/dL.

Potassium-sparing Diuretics

Potassium-sparing diuretics include spironolactone (Aldactone®), triamterene (Dyrenium®), and amiloride (Midamor®). These diuretics inhibit sodium reabsorption by acting on the cortical collecting tubules but may have an action on the outer medullary collecting tubules. The potassium-sparing agents induce a mild natriuresis to the extent of 2 to 3 percent of filtered sodium. Spironolactone acts by competing with aldosterone receptor sites. While amiloride has a pronounced effect in the presence of aldosterone, triamterene inhibits sodium reabsorption independent of aldosterone.

Dosage and Administration

Spironolactone: Usual does is 50 mg. Maximal dose is 400 mg/day in divided doses. The effect does not start until after 48 hours because of hepatic conversion to an active metabolite. Triamterene dosage: 50 mg twice daily to be increased to 100 mg twice daily. Amiloride dosage: 5 mg twice daily to be increased to 10 mg twice daily.

Adverse Effects

Spironolactone
- Hyperkalemia
- Gynecomastia
- Impotence
- Painful breasts and decreased libido in females

Triamterene
- Hyperkalemia
- Folic acid deficiency leading to anemia
- Triamterene renal calculi

Amiloride
- Hyperkalemia
- Hyperchloremic metabolic acidosis

Use of Potassium-Sparing Diuretic Can Lead to Life-Threatening Hyperkalemia Under the Following Conditions:

- Impaired renal function
- Concomitant use of ACE inhibitor drug
- Concomitant use of nonsteroidal anti-inflammatory drugs
- Underlying diabetic nephropathy
- Concomitant use of potassium, especially in t presence of low renal function

Carbonic Anhydrase Inhibitors

Acetazolamide (Diamox®) is a carbonic anhydras inhibitor. Acetazolamide acts in the proximal tubule an causes bicarbonate excretion, thus secondarily leads t sodium excretion and water diuresis. Because of chiefl bicarbonate diuresis, acetazolamide is recommende mainly in CHF associated with severe metabolic alkalosi Other indications of acetazolamide include elevated ur acid and uric acid or cystine nephrolithiasis. The goal i to keep urine alkaline, which will increase urinary uri acid and cystine excretion, respectively. Acetazolamid is a very common drug used for glaucoma.

Adverse effects of acetazolamide include hypokalemi hyperchloremic nonanion gap metabolic acidosi nephrocalcinosis, and nephrolithiasis.

Management Strategies of Refractory Edema and Anasarca

Refractory edema and anasarca are common in patient with chronic renal disease, CHF, and cirrhosis of live The underlying mechanism of refractory edema i hypoalbuminemia. Hypoalbuminemia is due to loss o albumin in the urine as in renal disease but also due t anorexia and poor intake of protein foods. As a result o profound hypoalbuminemia (albumin level <2.5 g/dL) filtered plasma stagnates in the interstitial space and, du to low pressure in the venous end of the capillaries, th filtered fluid becomes stagnant. The only way to dissipat this stagnant fluid is to give albumin infusion to increas the capillary pressure and increase renal perfusion an filtration rate. Diuretic resistance observed in thes patients is mainly due to poor renal perfusion. Diureti effect will be prompted by infusion of albumin.

Recommended Therapies for Refractory Edema

Normal renal function (serum Creatinine <1.5 mg/dL, eGFR ≥60 ml/min) A combination of a loop diuretic and a thiazide diuretic: 40 to 80 mg PO furosemide twice daily and metolazone 5 to 10 mg PO once daily. Potassium supplements and potassium-sparing diuretic, such as amiloride 2.5 mg PO twice daily, are essential to attenuate excessive potassium loss in the urine. Amiloride will also add to diuretic effect.

Oral diuretic therapy is ineffective in refractory edema with impaired renal function (serum creatinine >1.5 mg/dL and eGFR <60 ml/min), stage 2 to 3 chronic kidney disease. Intravenous boluses of furosemide or torsemide will induce diuresis, but overall effect is less than optimal. In such patients, a combination of furosemide or bumetanide and albumin infusion is likely to induce satisfactory diuresis with control of anasarca. Three to 5 liters of diuresis daily with this combination is not an unreasonable expectation. Previous studies have demonstrated that the combination of furosemide and human albumin solution can improve diuretic efficacy in hypoalbuminemic patients. Albumin expands blood volume and improves renal blood flow and, in addition, acts as a vector delivering furosemide to its site of transport. Author has found consistently expected results with a combination infusion of furosemide and albumin.

Furosemide or bumetamide infusion is very effective in anasarca associated with CHF as loop diuretic reduces left ventricular filling pressure and diminishes pulmonary venous congestion. That leads to relief from shortness of breath. Typically, furosemide 240 mg or bumetamide 12 mg is mixed in 500 ml of 5 percent dextrose in water. Potassium 20 to 40 mEq is added to the bag, depending on the renal function. The infusion is given at a rate of 21 ml/h, delivering 10 mg furosemide or 0.5 mg bumetamide per hour. Diuresis starts in less than 24h and reaches its peak in 72h. The rate of infusion is progressively titrated downward as diuresis is sustained. Albumin infusion is started at the same time at a rate 12.5 g every 6 to 8 hours and continues throughout the period of diuretic infusion.

Diuretic Infusion

A patient is illustrated here to demonstrate the effectiveness of diuretic infusion in a patient with generalized edema.

Patient Example

A 70-year-white male was admitted into a local hospital in Putnam County, Florida, on December 25, 2007, with a history of increased shortness of breath and 50 pounds weight gain in a short time. He also gave a history of alcoholism and cirrhosis of liver. He was propped up in bed, had anasarca and aortic stenosis, which led to CHF.

Medication at Time of Admission:

- Furosemide 40 mg po BID
- KCl 20 mEq po daily
- Metoprolol 25 mg po BID
- Digoxin 0.125 mg po daily

Laboratory upon Admission: December 25, 2007

Serum Chemistry	*Arterial Blood Gas Analysis*
NA 141 mmol/L	pH 7.45
K 4.9 mmol/L	PCO$_2$ 40.2 mmHg
Cl 107 mmol/L	PO$_2$ 73.0 mmHg
CO$_2$ 30 mmol/L	HCO$_3$ 28.1 mmol/L
BUN 47 mg/dL	Base Excess 4 mmol/L
Cr 1.55 mg/dL	O$_2$ saturation 95%
eGFR 47 ml/min	*Admission Treatment Comprised*
Total Protein 7.3 g/dL	Furosemide (Lasix®) 40 mg IV @ 12h
Albumin 2.4 g/dL	Oxygen inhalation 2L/min
Calcium 8.9 mg/dL	Metroprolol 25 mg po @ 12h
Total Bilirubin 1.1 mg/dL	KCl 20 mEq po daily
Digoxin 3.3 nano g/mL (high)	Allopurinol 100 mg po daily
January 3, 2008	*Serum Chemistry*
Albumin Infusion 25 g @ 6h x 4 doses	Na$^+$ 146 mmol/L
	K$^+$ 3.7 mmol/L
January 4, 2008 - nephrology consultation	Chloride 109 mmol/L
Physical Exam:	CO$_2$ 37 mmol/L
patient very weak with anasarca	Glucose 107 mg/dL
	BUN 26 mg/dL
	SCr 1.03 mg/dL
Laboratory	eGFR >60 ml/min
Hemoglobin 8.7 g/dL	Calcium 9.3 mg/dL
Hematocrit 26.4%	Phosphorus 3.3 mg/dL
	Magnesium 2.2 mg/dL
	Serum Ammonia 110 umol/L (n= 11-35)

Resurgent Therapy

1. Lasix® boluses were discontinued.
2. Started on Lasix® infusion (240 mg in 500 ml of 5 percent dextrose in water solution) at 21 ml/h (deliver

10 mg Lasix• per h). KCl 40 mmol was added to the bag (1.68 mmol K per hour).
3. Dopamine infusion at 1 mcg/kg body weight in 250 ml dextrose solution infusion was also run.
4. High protein, low salt diet was prescribed.
5. Procrit• 20,000 units subcutaneously every 48h until hemoglobin reaches 12 g/dL was prescribed.
6. He received transfusion of 2 units of packed cells.
7. Accucheck (glucose) every 6h and regular insulin coverage on a sliding scale was prescribed.
8. Albumin 12.5 g infusion every 8h x 10 doses were given.

Hospital Course is presented in Table 4.

Change of Therapy

1. Lasix• infusion reduced to 15 ml/h from 7 am January 7, 2008
2. Acetazolamide (Diamox•) 500 mg IV x 1st dose, then 250 mg IV every 8h x 3 doses were prescribed.
3. Half normal saline infusion at 50 ml/h, increased to 60 ml/h x 24h
4. Magnesium sulfate solution (50 percent): 2 ml (1g) deep 1m every 12h x 4 doses
5. Amiloride 2.5 mg po BID added

Change of Therapy

- Lasix• infusion decreased to 6 ml/h x 24h
- Continue half-normal infusion at 60 ml/h x 24h

Plans

1. Lasix• infusion discontinued
2. Amiloride discontinued
3. Discharge to home
4. Continue Procrit• 10,000 units subcutaneously once a week

Laboratory (Office Visit)
January 23, 2008
Hemoglobin 8.9 g/dL
Hematocrit 26 percent
Na^+ 143 mmol/L
K^+ 4.1 mmol/L
Chloride/CO_2 101/27 mmol/L
Glucose 102 mg/dL
BUN/Cr 20/0.92 mg/dL
eGFR >60 ml/min
Total Protein/Albumin 6.9/2.9 g/dL
Calcium 8.8 mg/dL
Phosphorus 3.3 mg/dL
Serum Ammonia 101 mmol/L

Plans

- Neomycin 500 mg po TID x 7 days
- Procrit• increased to 20,000 units subcutaneously once a week

Table 4. Hospital course after initiation of resurgent therapy

Date 2007-2008	*Bodyweight (pounds)*	*Urine Output (ml/24h)*	*Fluid Balance (– or +)*	*Renal Function (SCr mg/dL/eGFR ml/min)*	*Serum K mmol/L*
December 25	241	NA	NA	1.55 / 47	4.9
January 4	Resurgent therapy started				
January 5	235	3200	–1679	1.03/>60	3.6
January 6	221	5500	–3684	normal	normal
January 7	212	6525	–5585	normal	normal
January 8	209	NA	NA	reduced	4.3
Total weight reduction 39 pounds or 17.7 Kg in 4.5 days. Remission of anasarca. Near normal renal function and normal electrolytes. Serum albumin 3.2 g/dL.					
January 23 office visit	NA	NA	NA	0.92 / >60	4.1
NA = not available; – = negative balance.					

Office Visit

January 31, 2008	*Medication*
Feels well	Spironolactone 25 mg po once daily
Swelling of leg none	Furosemide 40 mg po BID
Ambulatory	Allopurinol 100 mg po daily
	Potassium Chloride 20 mEq p.o. daily
Bilateral Gynecomastia	Metoprolol 25 mg po daily
	Lactulose 30 ml po TID (for high ammonia)
	Procrit® 10,000 units subcutaneously once weekly

Refractory edema with severely impaired renal function: Serum creatinine >3 mg/dL, eGFR <30 ml/min stage 4 to 5 chronic kidney disease. At this stage of kidney function, diuretic boluses or diuretic infusion are minimally effective mainly due to inadequate delivery of diuretic at the site of an action in the nephron. Repeated albumin infusion, which helps delivery of diuretic at the nephron site, increases the risk of pulmonary edema. Therefore, at this state of renal function, recommended therapy is fluid removal by dialysis techniques. Two different types of dialysis are useful for adequate removal of fluid:

1. Intermittent hemodialysis
2. Continuous ambulatory peritoneal dialysis (CAPD)

Of the two above modalities, CAPD appears to be the more effective method of treating generalized edema and is done by the patients themselves; however, a support system is essential. Loss of albumin through CAPD exchanges, especially during peritonitis, is a serious drawback of this technique. In those with severe proteinuria and hypoalbuminemia, hemodialysis is preferable.

Use of ACE inhibitors in refractory CHF is a common practice, but its use is discouraged because these agents will cause further renal function deterioration, resulting in aggravated sodium and water retention and worsening of CHF. The ACE inhibitors markedly decrease the renal response of diuretic therapy. The improved heart function obtained by the use of ACE inhibitor parallel with decreased renal response is unable to promote diuresis. Hence, fluid and electrolytes imbalance worsen further to the detriment of the survival. Therefore, use of ACE inhibitors should be avoided until fluid and electrolyte control is secured by some form of dialysis.

Long-term Therapy

Long-term therapy of chronic edematous states consists of:

1. Restrict salt and fluid intake.
2. Wear stockings.
3. Keep legs clean and dry.
4. Seek medical attention if soreness, ulceration, or blisters are noted.
5. In case of males, use scrotal support to minimize scrotal swelling.
6. Use low dose thiazide diuretic, such as 12.5 to 25 mg hydrochlorothiazide or 2.5 to 5 mg metolazone daily.
7. Use spironolactone 25 mg once or twice daily or amiloride 2.5 mg once or twice daily in those with normal renal function to maintain normokalemia.

KEY POINTS

1. Generalized edema associated with ascites and pleural effusion is a fairly common nephrology consultation.
2. Renal function is variably impaired.
3. Hypoalbuminemia (serum albumin <3 g/dL) is a consistent accompaniment.
4. Hyponatremia and hypokalemia are common association.
5. Furosemide or bumetanide infusion is the most effective method of diuresis in generalized edema.
6. Concomitant albumin infusion enhances diuresis.
7. Replacement fluid in the form of isotonic saline —or half normal saline with added potassium—prevents renal function deterioration and hypokalemia.
8. Daily serum magnesium and phosphorus monitoring is recommended. Replacement is essential if levels are low.
9. Needless to emphasize are total attention and vigilant care. Nothing in the world can take the place of persistence.

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SECTION 2

DIABETES

- Diabetes: Logical Approach to Management of Diabetes with a Goal to Prevention of Complications
- Diabetes and Sexual Dysfunction: Etiology, Pathology, and Treatment
- Diabetes: What does High Glucose do to Body Function?
- Nondiabetic Renal Disease in Patients with Type 2 Diabetes Mellitus

12

Diabetes: Logical Approach to Management of Diabetes with a Goal to Prevention of Complications

Anil K Mandal

INTRODUCTION

By now you have developed a grasp of how much harm does high glucose (sugar), much higher than normal level (70 to 99 mg/dL / 3.8 to 5.5 mmol/L) cause to the various organs. Now is the time for the readers to know what can we do to bring down the sugar level and keep that to near normal level, so that anatomical and functional damage to the various organs can be minimized or prevented.

Since it is evident that high sugar level causes damage to the various organs, are there evidence that keeping the sugar level to normal level, as above, will completely prevent the damage (injury) or repair any damage that has already incurred. Ideally, from physiological standpoint, if elevated levels—whether it is sugar or urea or calcium—cause problem, that elevated level should be brought to normal level. However, it is important to know that it is difficult to achieve a normal level when it comes to sugar. Lowering the high sugar level to near normal level is a reality. The risk of hypoglycemic reactions is quite high when one attempts to lower the sugar to normal levels, such as close to 100 mg/dL (5.5 mmol/L) or hemoglobin A1c to less than 7 percent. Therefore, we have to reach a compromise in reaching a glucose level in our diabetic patients, whereby the organ damage can be halted or repaired and hypoglycemic reactions can be minimized. While no information is available with regard to ideal glucose level in a diabetic patients , there is subtle evidence that keeping 2-hour postprandial blood glucose (2h PPG) level to less than 200 mg/dL (<11.1 mmol/L) is beneficial. Again, the extent of benefit in proportion to a particular level below 200 mg/dL is undetermined. In other words, it is unknown if glucose level below 160 mg/dL (8.8 mmol/L) is more beneficial than that below 180 mg/dL (10 mmol/L).

On the other hand, the long-term consequences of repeated episodes of hypoglycemic reactions can be potentially serious. When sugar level drops to less than 50 mg/dL (<2.7 mmol/L), brain cell injury is a likely event. Here is an example: many patients above the age of 65 years are admitted to the hospitals with a diagnosis of altered mental state. Many such patients had a background history of diabetes and were treated with oral antidiabetic agents or insulin. Fluid therapy improves mental function in some, but not all, patients. Therefore, dementia in many such patients may be attributed to previous episodes of hypoglycemic reactions. This is not documented in the literature. This is author's general observation.

HINDRANCE TO CONTROL OF HYPERGLYCEMIA

Current classification of diabetes mellitus (DM) is the biggest hindrance to adequate control of diabetes. Here is a recapitulation of definition of DM in terms of levels of glucose (hyperglycemia).

Definition of Hyperglycemia (according to the American Diabetes Association)

a. Fasting blood glucose (FBG) ≥126 mg/dL (≥7 mmol/L)
b. 2hPPG ≥200 mg/dL (≥11.1 mmol/L) obtained randomly after a good meal or during an oral glucose tolerance test. The test should be performed as

described by the World Health Organization (WHO) using a glucose load containing the equivalent of 75g anhydrous glucose dissolved in water.

c. HbA1c ≥6.5 percent

The Type 1 DM encompasses the vast majority of cases that are primarily due to pancreatic islet B-cell destruction and that are prone to develop ketoacidosis. This form includes both children and unspecified number of adults. The Type 2 DM includes the most prevalent form of DM. Patients with this form of DM are generally overweight or obese and associated with high insulin response or insulin resistance. According to the authors, this form of DM is not truly diabetic. This classification provides no help in direct patient care. This classification only confuses the practitioners.

In the so-called Type 2 DM, pancreatic beta cells eventually undergo exhaustion or death due to spontaneous or dietetic overstimulation or that caused by the use of oral antidiabetic agents. Thus, the individuals who were showing a 2hPPG level of less than 200 mg/dL (<11.1 mmol/L) in the past suddenly begin to show a 2hPPG level above 200 mg/dL (>11.1 mmol/L). They are likely to have lost insulin response from dying pancreatic beta cells, thus leading to ***established diabetes***.

The worst fallacy in current diabetes care is to ascribe every adult with hyperglycemia automatically as Type 2 DM and hence prescribe oral antidiabetic agents. Two patients are presented here to clarify the fallacy in nomenclature. Author recommends to use the term ***"established diabetes"***—not Type 1 or Type 2 DM—when random blood glucose or 2hPPG is ≥200 mg/dL (≥11.1 mmol/L) in an individual irrespective of age or gender.

Patient Example 1

A 19-year-old white male, otherwise healthy, was admitted to a local hospital on April 13, 2009, with a diagnosis of diabetic ketoacidosis. Three days prior to hospital admission, he started to feel very thirsty, drinking too much fluid, and go to bathroom too many times. He felt very weak and tired. At 7:30 am on April 13, 2009, in the hospital emergency room, a random blood chemistry showed glucose 258 mg/dL (14.3 mmol/L), Na^+ 138 mmol/L, K^+ 2.9 mmol/L, CO_2 11 mmol/L, BUN 13 mg/dL (0.7 mmol/L), serum creatinine (SCR) 1.06 mg/dL (0.06 mmol/L), eGFR >60 ml/min, calcium 7.9 mg/dL (0.4 mmol/L), magnesium 1.9 mg/dL (0.1 mmol/L), hemoglobin A1c 12 percent. Average glucose (AG) was 298 mg/dL (16.5 mmol/L Urine was positive for glucose and ketones. A diagnos of diabetic ketoacidosis was made and he was treate with intravenous infusion of regular insulin along wit a sliding scale of regular insulin. His 24 h-urine protei was <255 mg. His glucose levels were brought to norm or near normal levels, and he was placed on a regime of Lantus® insulin 15 units after breakfast and 15 uni after dinner and regular insulin on a sliding scale. He wa followed in the office once and doing well. This patie represents typical Type 1 DM.

Patient Example 2

What about this patient—Type 1 or Type 2 DM? In 200 a 75-year-old WM went to a urologist's office for difficul in urination. A random blood chemistry showed glucos level between 300 and 400 mg/dL (16 to 21 mmol/L Patient was not aware that he has DM. He was sent t a primary care physician who considered that he ha Type 2 DM and placed him on the following medicatio Simvastatin 20 mg po daily, Furosemide 40 mg po dail Glucotrol XL 10 mg po daily, metformin (Glucophage 500 mg po bid, atenolol 25 mg po daily, and enalapr 10 mg po bid Severe hyperglycemia persisted, an he developed renal failure and hyperkalemia (seru potassium 5.9 mEq/L) and was admitted into a hospit on February 13, 2008. In the hospital, his rando glucose was 287 mg/dL (15.9 mmol/L), BUN 56 mg/d (3.1 mmol/L), Scr 2.42 mg/dL (0.1 mmol/L), eGFR 2 ml/min, triglyceride 583 mg/dL (32.4 mmol/L), an cholesterol 226 mg/dL (12.5 mmol/L). Prior to that, o May 14, 2007, his SCR was 1.21 mg/dL (0.06 mmol/ with an eGFR of 43 ml/min. Thus, his SCr doubled an eGFR decreased by one half in less than one-year perio due to a combination of uncontrolled hyperglycemia well as enalapril and furosemide combination therap Also, it became evident that his difficulty in urinatio was due to uncontrolled DM and not due to enlarge prostrate, which was the initial diagnosis.

Since hospital admission, oral hypoglycemic agent enalapril and furosemide, were discontinued. He wa placed on Lantus® insulin every 12h and regular insuli on a sliding scale. As of March 3, 2008, his 24 h proteinuri was 315 mg, 24 h creatinine clearance was 80.2 ml/mi His fasting glucose was 212 mg/dL (11.7 mmol/L), 2hPP 460 mg/dL (25.5 mmol/L), HbA1c 8.8 percent, Scr 1.7 mg/dL (0.09 mmol/L), and eGFR 41 ml/min. He receive

Lantus® 35 units 7:00 am and 40 units 7:00 pm (12h apart). He continues sliding scale of regular insulin. Here are his serial serum chemistry (Table 1).

Glucose control improved, which is associated with marked improvement in kidney function. Dosage of Lantus® insulin was adjusted upwards to achieve tighter glucose control.

Why did the primary care physician label him Type 2 DM, because of age or what? From author's perspective, this patient just has uncontrolled established DM with already manifestation of microvascular complications. Assigning a type of DM to an individual often depends on the circumstances present at the time of diagnosis, and many diabetic individuals do not easily fit into a single class. For instance, a person with gestational DM may continue to be hyperglycemic after delivery and may be determined to have, in fact, Type 1 DM. Another example would be a person treated with a thiazide diuretic who develops DM years later. Because thiazide diuretics, in themselves, seldom cause severe hyperglycemia, such individuals probably have Type 2 DM that is exacerbated by the drug. ***Thus, for the clinicians and patients, it is less important to label a patient with a particular type of DM than it is to understand the pathogenesis of hyperglycemia and treat it effectively.***

Control of Hyperglycemia and Monitoring of the Control

Utmost attention should be focused to identify and treat DM at the early stage when no complication has developed. ***Aggressive control of hyperglycemia with hypoglycemic agents, when complications have already developed, such as: renal failure, increases the risk of irreversible hypoglycemia and high mortality. A combination of long-acting and short-acting insulin is the cornerstone of therapy for control of hyperglycemia when blood glucose level is consistently above 200 mg/dL (>11.1 mmol/L).*** It is evident in the literature and everyday practice that tight control of blood glucose levels (2hPPG <200 mg/dL and HbA1c <7 percent) with insulin replacement therapy is fundamental to prevention of diabetic microvascular complications. On the contrary, slight or no information is available with regard to effectiveness of oral hypoglycemic agents in affording sustained control of hyperglycemia when blood glucose level is above 200 mg/dL (>11.1 mmol/L) and preventing microvascular complications. The patient #2 exemplifies that—

a. Technical pitfalls in control of hyperglycemia

   Most patients check their blood glucose before breakfast and before dinner—neither of which provides good information of glycemic control. In my office, patients are not familiar with 2hPPG checking. Literature information on 2hPPG testing is also scarce. Few studies have compared the validity of the glucose levels between two time periods (fasting and 2 hours after a meal) in relation to microvascular or macrovascular complications.

   HbA1c is most commonly obtained to determine glycemic control. However, HbA1c levels are not always parallel with individual glucose levels. Previous studies of the relationship between HbA1c and average blood glucose level (glycemia) have generally been hampered by limited measurement

Table 1. Serum chemistry of 75 WM

	Jan, 12, 2009 (Fasting)	*Mar, 2, 2009 (2h PP)*	*Jan 4, 2010 (Fasting)*
Glucose (mg/dL)/(mmol/L)	146/8.1	237/13.2	126/7
BUN (mg/dL)/(mmol/L)	18/1.0	18/1.0	15/1.34
SCr (mg/dL)/(mmol/L)	1.58/0.08	1.59/0.08	
eGFR (ml/min)	46	45	55
Na (mmol/L)	139	139	141
K (mmol/L)	4.6	4.7	5.0
Cl (mmol/L)	102	102	105
CO_2 (mmol/L)	29	29	30
Hemoglobin A1C/AV	8.5/197	n.d.	6.9/151

WM = white male, 2hPP = 2-hour postprandial, BUN = blood urea nitrogen, SCr = serum creatinine, eGFR = estimated glomerular filtration rate, Na = sodium, K = potassium, Cl = chlorine, CO_2 = carbon dioxide, n.d. = not done; AV = average.

of glucose values, casting doubt on the reliability of estimates of the AG value. A current study provides a relatively complete assessment of day-to-day glycemia and establishes a strong relationship between HbA1c and AG to justify a direct translation from HbA1c to an easier to understand glucose value that's in the same units as fingerstick glucose level. AG is not yet available in most laboratories. However, 2hPPG fingerstick levels can be reliably used to monitor glycemic control. I advise my patients to obtain fingerstick glucose level one to two hours after each meal and at bedtime and use regular insulin according to dosage on the sliding scale.

b. Compliance

It is imperative that we strive for early detection and treatment of DM, so that complications can be averted. Treatment of complications is costly; therefore, current huge health care costs for DM can be substantially reduced with early detection and treatment of DM. In 2009, annual diabetes-related spending among Medicare eligible population was $45 billion. In 2034, projected increase is $171 billion. There are programs to increase the awareness of DM, but these are few and far between. Notwithstanding increasing awareness, adequate funding for diabetes research, and plethora of oral medication to treat diabetes, complication rates are showing no sign of decrement. Here is an example: *The Los Angeles Times* as of March 22, 2009, reported "*over the last 15 years, the US rate of foot amputations from complications of diabetes has soared, approaching 100,000 annually, according to studies and government statistics.*" To that effect, both parties are responsible. Professionals are not emphasizing adequate glucose control with insulin therapy. A recent report indicates that only 17 percent of Type 2 DM patients take insulin. Another 17 percent of Type 2 DM patients take a combination of insulin and oral agents, whereas 54 percent are treated with oral agents. A 2004-2006 National Health Interview Survey is almost identical to the previous report. (See Figure 1)

Despite extensive efforts and more oral drugs available, attempts at reaching and maintaining near-normal glycemic levels in actual clinical practice have been largely unsuccessful. The unsuccesses are mainly due to lack of diet control and irregularities in taking prescribed doses of insulin. The most difficult part of satisfactory glucose control (see later) is refusal to adhere to a strict diet regimen. Here are some examples of noncompliance of diet control. Also diabetes care will improve if we identify patients as established diabetes and forget Type 1 or Type 2 diabetes, which adds nothing to overall diabetes care.

No. 1: 77 years obese white male with a long history of diabetes is regularly followed in the author's office. He was admitted in the hospital in the past for swelling of the lower extremity bilaterally. Over the years, his glycemic control has deteriorated as his kidney function. A blood glucose level 2-hours after lunch on December 17, 2009, was 435 mg/dL (24.1 mmol/L). He was admitted to a local hospital for glycemic control. In the hospital, he was treated with 1600 calories American Diabetes Association (ADA) diet, Lantus® insulin injection every 12 hours, and regular insulin every 6 hours on a sliding scale. On December 19, 2009, his fasting glucose was 173 mg/dL (9.6 mmol/L) and two hours after breakfast, it was 273 mg/dL (15.1 mmol/L). His kidney function was decreased in parallel with uncontrolled glucose level. The most recent office visit on February 25, 2010, showed fasting glucose of 223 mg/dL (12.3 mmol/L) and 2hPPG level of 342 mg/dL (19 mmol/L), despite he admits that he takes prescribed doses of insulin. His sugar control has

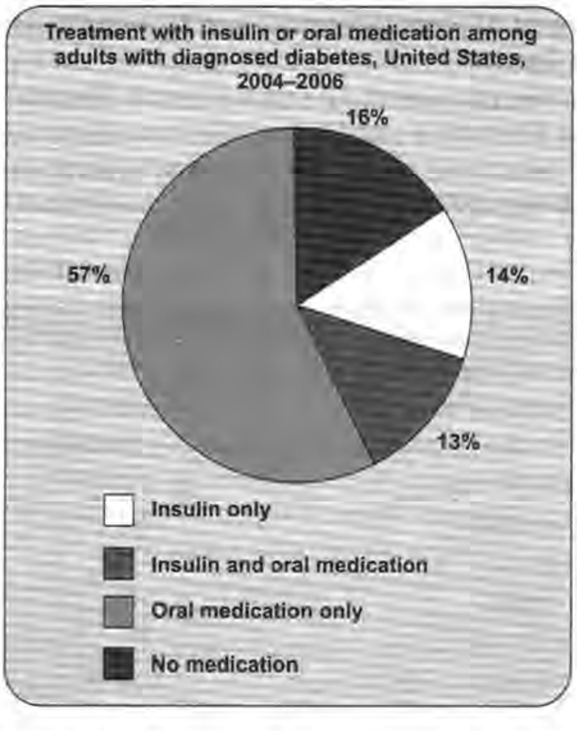

Figure 1: A 2004-2006 National Health Interview Survey

improved since December 17, 2009, but only marginally and kidney function improved also marginally. In the hospital, he was eating a prescribed diet that facilitated improvement in glucose control. At home, as before, he doesn't follow prescribed diet. Interestingly, his wife has told me that he doesn't follow prescribed diet. Thus, when she refuses to give him the foods he wants to eat, he goes out to a restaurant and eats what he likes to eat. He doesn't seem to care much about his glucose levels, even after knowing the consequences of elevated glucose levels.

No. 2: 69 years obese white female was admitted into a local hospital for evaluation of chest pain. A serum chemistry at 5:50 am (fasting) on September 19, 2009, showed glucose of 242 mg/dL (13.4 mmol/L). She was placed on a regimen of 1600 calories ADA diet and a combination of Lantus• and regular insulin. A blood glucose two hours after breakfast was 392 mg/dL (21.7 mmol/L). She admits that she adheres to diet therapy but in reality she does not.

No. 3: Here is a 78 years slightly obese white female with more than 30-years history of diabetes has been treated with diet control and insulin therapy. She lives with her daughter and son-in-law who prepare her food. According to her, they do not necessarily prepare her meals according to ADA diet; therefore, her sugar rises above desirable level. In the hospital on November 19, 2009, her fasting glucose was 111 mg/dL (6.1 mmol/L) and two hours after breakfast 224 mg/dL (12.4 mmol/L). Her two-hour level is slightly higher than where it should be. Although her kidney function is decreased but shows slight change over the years. She is essentially asymptomatic.

No. 4: 69-year old white male with a long history of diabetes.

- Treatment: Novolin N and Novolin R
- Problem: Cannot control foods

Jan 15, 2010	Fasting	344 mg/dL	(19.1 mmol/L)
	Bedtime	508 mg/dL	(28.2 mmol/L)
Jan 16, 2010	Before lunch	391 mg/dL	(21.7 mmol/L)
	After supper	386 mg/dL	(21.4 mmol/L)
Jan 20, 2010	Renal function	BUN mg/dL, SCr mg/dL, eGFR m/min	(32 / 1.81 / 40 mmol/L)

These patients illustrate that control of postprandial hyperglycemia is difficult to accomplish, because a large part of postprandial hyperglycemia is diet dependent. Glucose level is directly proportional to amount of food and type of food consumed. ***Therefore, diet control is an essential ingredient of diabetes care.***

It is also evident that obese people are more prone to higher glycemic level due to overeating and relative insulin resistance than other people who are not obese. One way to combat this problem is to adhere to a strict diet and author's advice is try your best to lose weight and to stay healthy.

There are some unrecognized factors that hinder glucose control and impair healthy life and daily performance. These include social stigma and affordability. Social stigma is very prevalent among patients with diabetes or hypertension. Patients are not able to accept or cope with the life style changes required in these illnesses. In underdeveloped countries, social stigma is even worse because patients feel embarrassed to go to doctors, thus delaying treatment. Similarly, regular sugar testing, special diet preparation, and long-term treatment program prove to be expensive to many individuals in underdeveloped and developing countries. Controlled diet therapy is more difficult in environment of multiple families living together in those countries. Personal or family income is often meager to buy required amount of insulin and diabetes supplies. Worst of all is lack of a refrigerator in many households. Thus, insulin kept in room temperature, which may be 90 to 100° F will lose its potency and effectiveness and not reduce blood sugar.

THERAPY FOR DIABETES

The most important therapy for diabetes is obviously replacement therapy, which is insulin. Satisfactory control of blood glucose levels (<200 mg/dL or <11.1 mmol/L) is the key to prevention of the microvascular and possibly macrovascular complications of DM and is more effectively accomplished with insulin than with oral drugs. Early insulin therapy with resultant satisfactory glucose control appears to spare or delay beta-cell damage and might even restore beta-cell function. Glucose control can be graded into the following three categories.

2hPPG Levels		
Satisfactory	= <200 mg/dL	(<11.1 mmol/L)
Fair	= 200-300 mg/dL	(11.1-16.6 mmol/L)
Poor	= >300 mg/dL	(>16.6 mmol/L)

Beta-cell function tends to decline over time in patients with Type 2 DM as insulin resistance leads to beta-cell exhaustion, and elevated lipids and glucose that exert toxic effects on beta cells.

The following approaches will permit to accomplish the most important goal of prevention of diabetic complications:

a. Satisfactory glucose control
b. Frequent office visits to maintain those controls

a. Satisfactory Glucose Control: Insulin Therapy

The authors concur with the approaches by Dr Palumbo to achieve treatment goals for DM. For patients with glucose levels lower than 200 mg/dL at diagnosis, the authors' recommendation is diet control (1800 calories, ADA diet), avoid excesses (buffet lunch or dinner, parties), and regular exercise with a goal to reduce weight for those who are overweight. Authors do not recommend oral agent(s), because oral agents lower fasting glucose and HbA1c but not 2hPPG level, as in the patients already presented.

For those with random (postmeal) glucose above 200 mg/dL or 2hPPG level above 200 mg/dL (>11.1 mmol/L), insulin is the cornerstone of therapy. Our experimental studies reinforce the clinical studies in that insulin therapy may reverse some effects of glucose toxicity, improving both insulin sensitivity and insulin secretion and reestablishing optimal control. This is in agreement with a previous report. A ten-year follow up of intensive glucose control in Type 2 DM indicates that intensive glucose control starting at the time of diagnosis is associated with a significantly decreased risk of myocardial infarction and death from any cause, in addition to the well-established reduction in the risk of microvascular disease. That study highlights the importance of glucose lowering in reducing the risk of coronary events and death from any cause. These findings strengthen the rationale for attaining optimal glycemic control and indicate emergent long-term benefits on cardiovascular risk.

A variety of insulin preparations is available: short-acting, intermediate-acting, and long-acting. Authors recommend sugar testing two hours after each meal, bed time, and upon waking in middle of night for satisfactory glucose control.

A study on delta glucose (2hPP-fasting) is linked to renal function changes (Mandal, Hiebert, Khamis, work is in progress). Preliminary results reveal significant correlation between delta glucose, SCr, and delta eGFR (estimated glomerular filtration rate) for all patients and when 2hPPG or postmeal glucose was greater than 200 mg/dL (11.1 mmol/L) but not when 2hPPG was less than 200 mg/dL (11.1 mmol/L). With delta glucose higher than 100 mg/dL (5.5 mmol/L), significant rise of SCr and significant decrease of eGFR is noted in those with 2hPPG above 200 mg/dL (11.1 mmol/L) but not in those with less than 200 mg/dL (11.1 mmol/L).

Principles of Insulin Therapy

Author recommends initiation of insulin therapy with a long-acting insulin. There are two types of long-acting insulin available in the market.

1. Insulin glargine (Lantus®), a recombinant DNA analog of human insulin, forms microprecipitates in subcutaneous tissue, delaying its absorption and prolonging its duration of action. Unlike NPH, lente, or ultralente (out of market in the USA), Lantus® has no peak concentration, thus mimicking continuous infusion of rapid-acting regular insulin from a subcutaneous pump.
2. Another long-acting insulin is detemir (Levemir®).

According to pharmaceutical companies, both Lantus® insulin and insulin detemir have similar onset of action in about four hours and reach their peak in eight to nine hours. Effect decreases after 12 hours. Which one of the long-acting insulins—Lantus® or detemir—to choose? Author prefers Lantus®, because he has more experience with that product. He recommends twice daily at 10 to 12 hours apart. There are no data to support or refute that long-acting insulin, such as Lantus® or Levemir® will be effective for 24 hours in those with normal kidney function. Why normal kidney function? Because insulin is excreted by the kidneys. In diabetes patients with decreased kidney function, insulin excretion will be reduced in proportion to decrease of kidney function. Thus, insulin dosage will be reduced proportionately and will be given at longer intervals. In these individuals, insulin will be retained in circulation and may cause irreversible hypoglycemia and a vegetative life. The author has already stated that it is important to reach a compromise of a glucose level (less than 200 mg/dL or 11.1 mmol/L) and thus reduce the risk of hypoglycemia. Accord study results indicate that aggressive HbA1c target (<6 percent) may not be beneficial in patients with existing cardiovascular disease and a longer duration of diabetes. In the latter, patient's renal function is generally reduced, thus risk of severe hypoglycemia and vegetative life is quite high, if one attempts to treat aggressively to reduce HbA1c to less than 6 percent even less than 8 percent. This was not an appropriate study to do.

It is important for the readers to know that Lantus® or Levemir® taken twice daily after breakfast and dinner (12 hours apart) has made a big difference in attaining satisfactory glucose control among his patients in the office and in the hospital where author is a consultant. Here is one such example.

A 56 years white female was seen in consultation on February 17, 2010, for acute elevation of blood glucose and renal insufficiency. On history taking and physical examination, her main problem is bilateral foot ulcer under the heel: one is necrotic looking, and the other not so bad looking. She had already her right great toe amputated. She gives history of diabetes for 26 years. She has had no other complaint. She was taking Lantus® insulin once a day and regular insulin on a sliding scale. She had persistently poor glucose control. Here are some of the records.

February 16, 2010	366 mg/dL	(20.3 mmol/L)
January 2006	500 mg/dL	(27.7 mmol/L)
November 4, 2006	518 mg/dL	(28.7 mmol/L)
November 5, 2006	442 mg/dL	(24.5 mmol/L)
September 2009	517 mg/dL	(28.7 mmol/L)
	489 mg/dL	(27.1 mmol/L)

In the hospital, she was started on Lantus® insulin after breakfast and after dinner (12 hours apart) and Novolog® on a sliding scale. She was discharged on February 19, 2010. She recorded her sugar one hour after breakfast, lunch, and dinner (Table 2). Only three levels were over 200 mg/dL after breakfast and one each after lunch and dinner from March 5 to 25, 2010. In a total of 60 readings, only one level was 300 mg/dL (16.6 mmol/L). She takes Lantus® insulin 20 units after breakfast and 20 units after dinner and Novolog® according to sliding scale.

As of February 20, 2010, her kidney function is reduced. The estimated glomerular filtration rate was 35 ml/min, and HbA1c was 11.5 percent. She has had no sexual desire and doesn't participate in a sexual activity with her husband. Her husband is very angry because he doesn't understand the problem. Finally, this patient exemplifies that foot ulcer, gangrene and amputation, rapidly deteriorating kidney function, and sexual dysfunction are the ultimatum of uncontrolled glucose level in the range of 300 to 500 mg/dL or higher.

Table 2. 59 WF: Home monitoring of fingerstick blood glucose levels

	Breakfast	***Lunch***	***Dinner***
3-5-10	96	151	143
3-6-10	123	115	136
3-7-10	**150**	165	146
3-8-10	161	110	144
3-9-10	88	160	**238**
3-10-10	109	75	128
3-11-10	**300**	130	109
3-12-10	**151**	129	110
3-13-10	120	111	89
3-14-10	139	191	125
3-15-10	155	173	98
3-16-10	**205**	**181**	103
3-17-10	48	75	120
3-18-10	111	162	113
3-19-10	71	**225**	151
3-20-10	**265**	112	170
3-21-1-	61	1.05	182
3-22-10	85	160	93
3-23-10	52	152	65
3-24-10	**146**	104	182
3-25-10	86		
3-26-10			
3-28-10			
3-28-10			
3-29-10			
3-30-10			
3-31-10			

WF = white female.

A list of rapid-acting, short-acting, intermediate-acting, and long-acting insulin preparations with onset of action, peak action, and duration of action are presented in Table 3 for convenience of the readers.

While Lispro is very rapid acting (action starts within 15 to 30 minutes), regular insulin, such as Humulin R or Novolin R, also is fast and action starts within 30 to 40 minutes. It is not necessary to use ultrafast-acting insulin, which offers no advantages over and above regular insulin. Furthermore, risk of hypoglycemia can be higher than with regular insulin.

Intermediate-acting insulins are NPH (Neutral Protamine Hagedorn), Humulin N, and Novolin N. Then there are 70/30 mixed insulins. These 70/30 insulins are mixture of intermediate-acting and short-acting insulins. The author considers no special advantages of using intermediate-acting insulin, and he does not recommend that. Insulin effect is reduced by mixing different types of insulin and is not recommended.

Table 3. Onset, peak, and duration of insulin types

Insulin Types	*Onset of Action (hours)*	*Peak (hours)*	*Duration (hours)*
Rapid-acting:			
Lispro† (Humalog)	0.25 – 0.5	0.75 – 2.5	<5
Short-acting:±			
Regular	0.5 – 1.0	2.5 – 4	6 – 8
Intermediate-acting:			
NPH±	1.5	4 – 12	18 – 24
Lente±	2.5	7 – 15	22 – 24
Premixed:			
(Regular/NPH)	0.5	2 – 12	18 – 24
30/70	0.5	1 – 12	18 – 24
Long-acting:			
Ultralente	4	8 – 24	24 – 28
Glargine** (analogue)	1 – 2	flat / smooth	24

† Humalog has twice the peak maximum concentration of regular insulin. Humalog should be taken ≤ 15 minutes before eating.

± These insulins work best if injected -1/2 hour prior to the meal.

** Not available in Canada.

Insulin Regimen as Proposed by the Author

Regimen 1. All diabetic patients, when they are first seen in author's office, can be divided into following groups. Group 1: Not on insulin but taking multiple oral antidiabetic agents. These are glyburide, metformin, Januvia•, glimepiride. Group 2: As above plus a small dose of regular or Lantus• at bedtime. Group 3: Lantus• 10 to 15 after breakfast or at bedtime. No coverage throughout the day. In many of these patients, fasting or random (postmeal but exact postmeal hour not known) glucose ranges between 200 and 300 mg/dL (11.1 and 16.6 mmol/L). Author makes no change in their therapy at the first visit. However, if a patient at a first or subsequent office visit reveals random or 2hPPG over 300 mg/dL (16.6 mmol/L) and decreased kidney function, such as elevated BUN and SCr levels, author urges hospital admission to bring glucose level to less than 200 mg/dL (11.1 mmol/L) and to create a regimen to keep the sugar level at that range. The main objective of doing that is to protect kidney function from further deterioration and reduce the risk of entering into dialysis.

Regimen 2. Patients not exposed to insulin therapy, have been treated with multiple oral antidiabetic agents, but find glucose levels going very high. The latter scares them and increases their interest to start on insulin. Before author recommends or starts on insulin therapy, he explains the risks and benefits of insulin therapy. The risks are minimal and mainly slight pain from injections, scarring, and discoloration of the skin from repeated injections. These skin changes are mostly cosmetic but pose no threat to life. Skin infection from insulin injection is rare, if the same needle is not used more than once and skin is cleaned with alcohol swab before and after injection. Skin infection, such as furuncles and carbuncles, are common only in those with severely uncontrolled diabetes and living in unhygienic conditions, as in underdeveloped countries. Slight weight gain is a common place with insulin therapy but is not a concern for active individuals. Notwithstanding these minor risks, the benefits of insulin therapy are overwhelming, mainly due to its insurance against the horrible complications of uncontrolled diabetes (mentioned throughout the book). Once again, satisfactory glucose control is achievable only with insulin therapy and is an insurance against foot ulcer, gangrene, and amputation, progressive kidney failure, erectile dysfunction, and heart attack.

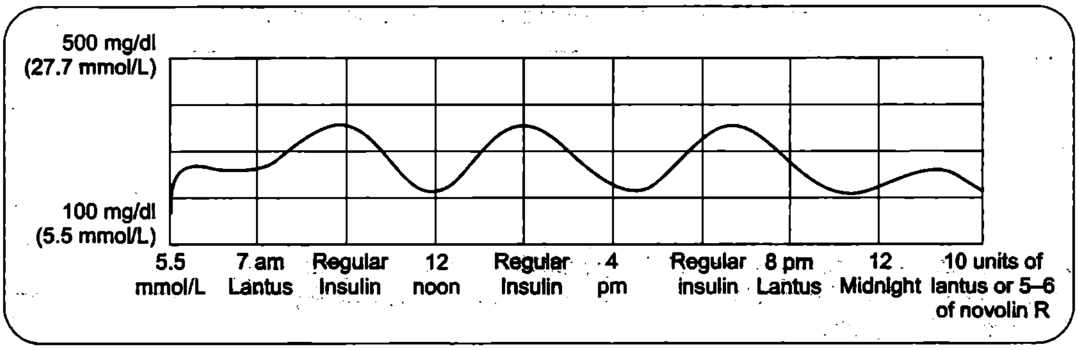

Figure 2: Schematic diagram of postmeal glucose surges

Initiation of Insulin Therapy

Here is how the author initiates insulin therapy. He starts with 10 to 20 units of Lantus* insulin, depending on 2hPPG level after breakfast and after dinner with 12 hours apart between the two injections. This dosage is increased at an interval of three to four weeks until satisfactory glucose control is achieved. Most patients need additionally regular insulin, such as Novolin R, according to sliding scale. Author recommends a standard sliding scale, which is as follows:

Fingerstick Glucose Level		*Novolin R*
mg/dL	*mmol/L*	*in units*
150 – 200	8.3 – 11.1	4
201 – 250	11.1 – 13.8	8
251 – 300	13.8 – 16.6	12
301 – 350	16.7 – 19.4	16
351 – 400	19.5 – 22.2	20

Above 400, author advises that patients call his/her own primary doctor or author himself for admission into a hospital and undergo investigation to determine the cause of uncontrolled hyperglycemia.

Uncontrolled hyperglycemia is most commonly due to the failure to adhere to a prescribed diabetic diet intentionally or otherwise. However, even in best of circumstances, uncontrolled hyperglycemia could be due to urinary tract infection, flu, or pneumonia, in and of itself, as well as a result of failure to take prescribed doses of insulin due to the illness. Treatment of these incidental conditions along with aggressive insulin therapy help to restore good glycemic control.

Monitoring of Glycemic (Glucose) Control

There are many ways to monitor day-to-day glucose control. Fingerstick glucose levels by the patients themselves are by far the best. Continuous Glucose Monitoring (CGMS), which are a new technology, was compared to self-blood glucose monitoring. Evidence was insufficient in support of superiority of CGMS over self-fingerstick glucose level in monitoring glycemic control. Traditionally, most patients have done or still do sugar testing at fasting and before each meal. Author recommends to check one to two hours after each meal, at bedtime, and upon wake up in the middle of night. The most important glucose level to watch is the postmeal surges. These postmeal surges can cause profound vascular damage. Here is a schematic diagram (Fig. 2).

Glucose levels run like peaks and valleys (schematic diagram). Lantus* twice daily will keep the valleys under control. Peaks need to be encumbered by regular insulin, such as Novolin R*. Although it is generally considered that peaks are harmful, no study was ever done to determine if the valleys are harmless. Author recommends patients to record all glucose readings and bring those recordings to office during scheduled visits. He reviews with the patients their recording of glucose levels less than 200 mg/dL (<11.1 mmol/L) and more than 200 mg/dL (>11.1 mmol/L) and compares those levels with laboratory reports of fasting and 2hPPG levels, HbA1c, and AG levels. It is a tedious job both for the patients and the doctors to keep up with the monitoring of glucose control. The tediousness of glucose monitoring compel patients and the doctors to resort to alternative method of glycemic control via oral antidiabetic agents with or without the full knowledge that oral antidiabetic agents may lower glucose levels as much as insulin, but these agents afford no or slight protection against the vascular complications. For the convenience of the readers, glycemic control in diabetes (United States) is shown below in Table 4.

Table 4. Glycemic control in diabetes (united states)

Index	*Goal*	*Action Recommended*
Fasting or preprandial	80-120 mg/dL (4.4-6.6 mmol/L)	<80 or >140 mg/dL (<4.4 or >7.7 mmol/L)
2-hour postprandial	180 mg/dL (10 mmol/L)	>180 mg/dL (10 mmol/L)
Bedtime	100-140 mg/dL (5.5-7.7 mmol/L)	<100 or >160 mg/dL (<5.5 or >8.8 mmol/L)
HbA1c*	<7	>8

* Laboratory terminology for a specific hemoglobin component of glycosylated (glycated) hemoglobin.
Adapted from American Diabetes Association. Position statement: standards of medical care for patients with diabetes mellitus. *Diabetes Care* 1998;21(suppl 1):S24.

Early Morning Glycemic Surge

Early morning glycemic surge giving rise to fasting hyperglycemia is not uncommon even in the best of hands. This fasting hyperglycemia is a part of early morning hormonal surge, such as high cortisol or epinephrine and norepinephrine level. In hypertensive patients, blood pressure peaks are common in early morning hours. Therefore, it is prudent to state that these hormones surges increase blood pressure as well as blood glucose levels. Epinephrine causes glycogenolysis by converting liver glycogen into glucose. These hormones also inhibit uptake of glucose by the liver. Apparently, liver plays an important role in fasting and postprandial hyperglycemia. However, the pathways of the interactive role of liver in sustaining hyperglycemia are not yet elucidated. Author feels that until we know more about liver's role in early morning glycemic surge, it is appropriate to use an extra dose of 10 units of Lantus® or 5 to 6 units of Novolin R® at bedtime, which may mitigate early morning hyperglycemic surge.

Interestingly, this early morning hyperglycemic surge is conducive to good sleep; whereas, taking an extra dose of insulin at bedtime may increase the risk of hypoglycemic reactions. One of the hypoglycemic reactions is waking up in the early morning with perspiration or with an urge to go to bathroom. Perhaps the severity of hypoglycemic reactions may be reduced with fine adjustment of bedtime insulin over a period of time and consuming six to right ounces of juice or milk before going to bed.

Decisive Indication of Insulin

1. 2hPPG >200 mg/dL (>11.1 mmol/L) x 2 irrespective of FBG.
2. 2hPPG <200 mg/dL (<11.1 mmol/L) with evidence of one or more organ damage. These are as follows:
    a. Proteinuria/decreased kidney function
    b. Erectile dysfunction or decreased libido i
    females
    c. Urinary retention
    d. Decreased vision
    e. Coronary artery disease
3. Pre- and postsurgical condition
4. Pregnancy and Postpartum
5. Aggressive hyperglycemia caused by steroid therapy or an immunosuppressive drug, such a tacrolimus.

Assessment of Outcome Measures in Office Practice

Improvement by Diabetes Therapy

1. Initial Laboratory
2. Insulin vs. Oral Agents
   plus prescribed diet and weight reduction
3. Follow-up Laboratory: every 8 to 12 weeks
    - Order: a. Urinalysis
      b. Fasting and 2hPP basic metabolic panel
      c. HbA1c (will give you AG)
    - Measure sexual function (most neglected area)
    - Check feet
    - For vision, refer to an ophthalmologist
    - Assess ischemia of heart by ECG or refer to a cardiologist

Assessment of Erectile Dysfunction/Improvement

Dysfunction = no erection

Improvement = 4+ sustained erections and achieve sexual intercourse

Remember: *Diabetes is the most common cause of erectile dysfunction.*

Insulin versus Oral Antidiabetic Agents

You convince yourself, first, which of the two modalities of therapy - insulin or oral antidiabetic agents - is most effective in:

1. Reducing proteinuria
2. Stabilizing or improving renal function
3. Preventing blindness
4. Preventing gangrene
5. Restoring sexual function
6. Preventing heart attack

Refusal to Take Insulin will Always be a Problem

We have to work hard to convince patients that insulin will oxidize glucose and give you the energy that you need and protect you from horrible complications, whereas oral drugs will not. First convince yourself; then convince the patients.

An Important Prevention Strategy

What will you do to increase the number of diabetic patients taking insulin? Here is one idea:

Volunteerism by insulin-treated patients who understand that satisfactory glucose control with insulin is permissive of a healthy life. Such insulin-treated patient-volunteers could counsel patients who refuse to take insulin.

Oral Hypoglycemic Agents

A big list of oral hypoglycemic agents is presented in Table 5. One or more than one oral hypoglycemic agents can be used in those with 2hPPG level consistently less than 200 mg/dL (<11.1 mmol/L). Oral hypoglycemic agents are unsafe in those with acute or chronic renal failure because of irreversible hypoglycemia. ***Metabolic acidosis of variable severity is another complication of metformin. Metabolic acidosis can be a serious threat in those with impaired renal function.***

However, in those with 2hPPG above 200 mg/dL (>11.1 mmol/L), oral antidiabetic agents can be used in addition to insulin to achieve better glucose control than either alone but with no additional benefit. Two studies are cited to that effect:

1. 390 patients, treated with insulin in the outpatient clinics of three hospitals in a randomized placebo-controlled trial with a follow-up period of 4.3 years, were entered into a study. Metformin 850 mg or placebo (one to three times daily) was added to insulin therapy. The primary end point was an aggregate of microvascular and macrovascular morbidity and mortality. The secondary end points were microvascular and macrovascular morbidity and mortality, as separate aggregate scores. Metformin treatment prevented **weight gain**, improved glycemic control (mean reduction in HbA1c 0.4 percent), and reduced insulin requirement, but did not improve the primary end points. Metformin did, however, reduce the risk of macrovascular disease after a follow-up period of 4.3 years.
   a. In a study from Kolkata, India, 312 patients with diabetes were treated with insulin (n=23), oral hypoglycemic agent (OHA) (n=262), insulin+OHA (n=27). Paired fasting glucose (FG), 2hPPG, and eGFR were obtained before and after 12-month period. Mean percent decreases in FG and 2hPPG levels were significantly better in insulin+OHA group when compared with OHA alone, but eGFR percent change was significantly higher in insulin group than in other two groups (Patnaik A, Mandal AK: unpublished).

   It is well-known that insulin causes weight gain. Therefore, except to prevent weight gain, use of metformin thus far has no added benefit over and above insulin therapy in preventing microvascular complications in DM patients.
2. Acarbose. The only oral antidiabetic agent author recommends is acarbose. He recommends acarbose in combination with insulin in obese and diet noncompliant patients. Acarbose is an alpha-glucosidase inhibitor, which competitively inhibits the alpha-glucosidase enzymes in the gut that digests dietary starch and sucrose. Two of these drugs—acarbose and miglitol—are available for clinical use. Both drugs delay the absorption of carbohydrate and lower postprandial glycemic surges. Acarbose is available as 50-mg and 100-mg tablets. Author starts as 50 mg with breakfast, lunch, and dinner but increases to 100 mg with lunch and dinner to minimize postprandial hyperglycemic surge. The common side effect of these drugs is flatulence. This is caused by undigested carbohydrate reaching the lower bowel, where gases are produced by bacterial flora. In small number of patients, troublesome diarrhea may develop, requiring discontinuation of the drug. A slight increase in liver enzymes

Table 5. Oral hypoglycemic agents*

Medication	*Class*	*Mode of Action*	*Targeted Organ(s)*	*Usual Starting Dose*	*Usual Maintenance Dose*	*Recommended Maximum Daily Dose*
Acetohexamide Dymelor®	1st generation sulfonylurea	Stimulates secretion of insulin by pancreas	Pancreas	250 mg	250-1,500 mg/day before meal	1,500 mg
Chlorpropamide Diabinese®				100-250 mg	100-500 mg/day	750 mg
Tolazamide Tolinase®				100-250 mg	100-1,000 mg/day with meal	1,000 mg
Tolbutamide Orinase®				1,000-2,000 mg	250-3,000 mg/day (divided)	3,000 mg
Glimepiride Amaryl®	2nd generation sulfonylurea	Stimulates secretion of insulin by pancreas	Pancreas	1-2 mg	1-4 mg once daily (with meal)	8 mg
Glipizide Glucotrol® Glucotrol XL®				5 mg	5-40 mg/day (once or divided pre-meal) XL formula, once daily	40 mg XL formula, 20 mg
Glyburide Diabeta® Micronase®				1.25-5 mg	1.25-20 mg, once or divided twice a day before meal	20 mg
Glyburide, micronized Glynase Pres Tab®				1.5-3 mg	0.75-12 mg, once daily or divided with meal	12 mg
Repaglinide[†] Prandin®	Meglitinide (nonsulfonylurea portion of glyburide)	Stimulates secretion of insulin by pancreas	Pancreas	0.5-2 mg	0.5-4 mg 15 min before meals (up to 4 times/ day) . MUST eat after dose	16 mg
Metformin[±] Glucophage®	Biguanide	Decreases heptatic glucose production & intestinal glucose absorption; improves insulin sensitivity	Liver, peripheral tissues, small intestine	50 mg twice/day or 850 mg/day (with meals)	850 mg 1-2 times/day to 850 mg 3 times/day (with meals)	2,550 mg
Rosiglitazone[§] Avandia®	Thiazolidinedione	Directly decreases insulin resistance; increases glucose disposal	Muscle & adipose tissue, liver, peripheral tissues	4 mg/day (once or divided) with or without food	4-8 mg/day as single dose or divided twice a day with or without food	8 mg
Pioglitazone Actos®				15-30 mg once daily with or without food	15-45 mg once a day with or without food	45 mg
Acarbose Precose®	Alpha glucosidase inhibitor	Delays absorption of glucose from GI tract	Small intestine (enzyme inhibitor)	25 mg 3 times/day (with first bite of meal)	50-100 mg/day (divided 3 times/day)	300 mg
Miglitol Glyset®						

* All above medications are primarily used in conjunction with dietary control, weight loss program, exercise program, and stress management.

Sick-day management: remember to take medication as prescribed and proper dietary intake.

Travel tips: Carry all medication with you; do not pack in luggage; keep in original prescription bottles.

† Repaglinide (Prandin), since this agent lowers the blood sugar load from the current meal, do not take a dose if a meal is going to be missed. Check with physician regarding specific instructions a=bout skipping or adding meals.

± Metformin (Glucophase) should be stopped (at the time of or prior to) and withheld for 48 hours after any procedure involving systemic, iodine-based radiocontrast media.

§ Baseline and periodic liver function tests required for rosiglitazone (Avandia) and pioglitazone (Actos®).

This information was compiled from medication package inserts for general reference use.

may be observed, requiring dosage reduction or discontinuation of the drug.

Diet Alone

Diet control alone works in achieving glycemic control. Here is a 60-year-old white female weighing 237 lbs. was seen in consultation in author's office on November 23, 2009, for decreased kidney function. She has a history of diabetes and hypertension for 10 years. She was treated with Accupril® (ACEI) 40 mg tablet daily, hydrochlorothiazide 25 mg one daily (which always increases glucose level mimicking diabetes), Lipitor® 40 mg daily for hyperlipidemia, and fluoxetine 20 mg daily for depression. She didn't have any laboratory done except the information that her kidney function was decreased. A glomerular filtration rate of 46 ml/min (normal >60 ml/min) was reported. Author discontinued accupril, which has decreased her kidney function. He also discontinued hydrochlorothiazide, which probably changed prediabetes into diabetes, and started her on methyldopa to control hypertension. She returned on December 30, 2009. Her fasting glucose was 168 mg/dL (9.3 mmol/L). AG was 209 mg/dL (11.6 mmol/L) and HbA1c 8.9 percent. She didn't receive any antidiabetic therapy. She follows diet therapy. She also has left breast cancer and is treated with chemotherapy and irradiation. Author instructed her to check glucose level one to two hours postmeal. She returned on March 17, 2010, and brought her readings. All postmeal readings were less than 200 mg/dL (<11.1 mmol/L) except one when she ate pie and glucose went up to 214 mg/dL (11.8 mmol/L). Her kidney function improved to almost normal level; eGFR was 57 ml/min (normal >60 ml/min). At best, this patient is prediabetic, but drugs like hydrochlorothiazide can tip off her glycemic control and can cause established diabetes. Author prescribed acarbose 50 mg to take with each meal to supplement diet control and reduce weight. Insurance did not pay for the medicine. It is evident that insurance companies are hindrance to effective diabetes management and prevention of its complications.

HYPOGLYCEMIA

Normal laboratory range of glucose is 70 to 99 mg/dL (3.8 to 5.5 mmol/L). Blood glucose of 10 to 20 mg/dL (0.5 to 1.0 mmol/L) below the lower range of normal can produce hypoglycemic symptoms. All insulins, including long-acting insulins, can cause hypoglycemia. Hypoglycemic reactions are more common with short-acting or ultra-short-acting insulins than with long-acting insulins. Lantus® insulin alone is less likely to cause hypoglycemic symptoms. OHAs can cause protracted hypoglycemia, particularly in elderly patients and in those with impaired kidney or liver function. It has been shown that glyburide appears to cause a higher incidence of hypoglycemia than chlorpropamide, glipizide, or glimepiride.

Most commonly, blood sugar decreases fast and to a very low level when you haven't eaten well and have taken insulin and immediately engaged in a physical activity. Physical activity adds to hypoglycemic effect of insulin or OHAs.

The earliest symptoms of hypoglycemia are blurring of vision with inability to read small letters, unsteadiness or feeling weak in standing or walking, and feeling loss of balance. Waking up from sleep drenched in sweat is also common. Difficulty in falling into sleep, feeling nervousness, and feeling excessively hungry are other common symptoms.

Relief of Hypoglycemic Symptoms

The fastest way to obtain relief is to drink eight ounces of orange juice with one or two pieces of bread or with cookies. The solid food holds orange juice for its steady absorption. Concomitantly with the above, it is imperative not to be engaged in physical activity for 15 minutes. Eight ounces (200 ml) orange juice contains twenty grams of sugar. Each gram of sugar in the juice may increase blood sugar by 5 mg/dL (0.2 mmol/L). Apple juice or pineapple juice of same volume is also effective, but relief of symptoms with orange juice is faster than other juices. Eight ounces of milk with a peanut butter sandwich is also effective. Patients with diabetes will learn over the years by trial and error which of the foods will relieve their symptoms most and in a fastest way. One hour after hypoglycemic episode, fingerstick glucose level may be ≥200 mg/dL (≥11.1 mmol/L). Therefore, it is time again to take a low dose of regular insulin to prevent glucose levels keep rising. It is important that diabetic patients carry juices, cookies, or crackers at all times while driving or traveling in a bus, train, or airplane and carry a tag as diabetic in case serious symptoms develop and require emergency attention, such as intravenous infusion of 50 percent dextrose solution to promptly increase blood sugar to near normal to normal level (70 to 99 mg/dL).

In summary, keeping glucose level at the normal range, as stated above, for people who have diabetes is an unreality. Even by taking insulin multiple times, glucose level may reach normal level but only for a short time, because endogenous insulin response is insufficient. Manipulation by oral antidiabetic agents to enhance endogenous insulin release or increase insulin sensitivity results in exhaustion of the beta cells, leading to easily controllable glycemic state to a pathological uncontrollable glycemic state over the years. Even more troublesome is the lack of established information about the glucose levels that are safe for patients who have diabetes. By the term safe glucose level, the author means a glucose level that is least toxic to microvascular system and not likely to cause neuropathy, foot ulcer, gangrene, sexual dysfunction, and kidney failure. To achieve that glucose control is a formidable task for the patients as well as the doctors and nurses. Nevertheless, **persistence** is essential in diabetes management. Thus, on one hand patients must be astute in their care and doctors and nurses must be diligent in implementing and maintaining optimal glucose control in their patients. Both parties must be cohesive to achieve only one goal, which is to keep patients learn to cope with diabetes and thrive.

Here is a story from Bill and Rose about when to take insulin. I hope this story should be a revelation for those who delay in accepting insulin therapy or refuse to take insulin.

When Bill learned he had diabetes, his first treatment was the basics: lose a little weight and start to exercise. That worked for quite a while. When Bill and his doctor noticed his A1C was starting to creep up toward 8 percent, they decided it was time to start a pill to get his blood sugar in a safer range. That worked for quite a while too. When Bill's A1C was starting to climb again, they added another pill. When Bill noticed his blood sugar was often topping 200 mg/dL, he wondered what would be next.

Bill started looking for answers with his older sister, Rose. She had been living with diabetes for 10 years before Bill was diagnosed. Rose had been on insulin for several years. She told him giving herself an insulin shot hurt far less than poking her finger to test her blood sugar. Rose said she had gained a little weight when she started insulin. Once she got her healthy eating plan and insulin routine matched, she dropped those extra few pounds.

Bill asked his diabetes educator if starting insulin meant his diabetes was now the serious kind of diabetes. She said, "No, you just need a better way to get your blood sugar in control." She explained that as the body becomes less able to make enough of its own insulin to keep blood sugar levels where they should be, even with the help of pills, taking insulin makes sense. She offered to help him get started if Bill and his doctor decided Bill should start using insulin.

When Bill went to see his doctor, Bill asked him the same questions. Bill and his doctor decided that the time was right to start insulin, and Bill was ready. He had prepared himself to take charge of his health. Bill wanted to be there for his little grandkids as they grew up!

Use of Renin-Angiotensin Inhibitor Drugs in Diabetes

Use of angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocking (ARB) group of drugs has no place in the diabetes management. Three patients are presented here to illustrate the serious problems associated with use of ACEI/ARB group of drugs (Tables 6, 7, 8).

The worst problems associated with use of ACEI or ARB are severe metabolic acidosis and hyperkalemia, which can be life-threatening. Renal protection was attributed to slight change in SCr but profound decrease in creatinine clearance, as shown in this patient (Table 9). Proteinuria in diabetic and nondiabetic renal disease is a prevalent issue in current medical practice that is associated with increased pressure to treat proteinuria, including microalbuminuria with ACEI, ARB, or a combination of both drugs. The medical literature is filled with publications supporting the use of these drugs. The premise in these publications is that reduction of proteinuria will delay the progression of diabetic renal disease into end stage renal disease (ESRD). Decrease of proteinuria is secondary to decrease in creatinine clearance, as exemplified in Table 8. As will be noted that with 0.1 mg increase of SCr, creatinine clearance decreased by 26 ml/min, creatinine clearance was rarely reported in most or all publications that were proponents of the use of ACEI/ARB. These are few of numerous patients who developed acute renal failure, metabolic acidosis, hyperkalemia, and anemia associated with use of ACEI or ARB or a combination of both drugs.

Table 6. Serial laboratory studies in 54 wf with a history of DM for 52 years

Date 2003-2005	Glucose mg/dL	BUN mg/dL	SCr mg/dL	Na* mEq/L	K* mEq/L	CO_2 mEq/L	Hb g/dL	Hct %
May 29, 2003	139 (F)	71	2.4	137	4.3	33	na	na
May 29, 2003	**Accupril discontinued**							
July 7, 2003	95 (F)	21	1.2	143	4.2	27	11.9	36.4
Nov 28, 2003	115	32	1.2	136	3.6	23	12.6	36
Dec 31, 2003	> 503 (A)							
	Hospital admission							
Jan 1, 2004	> 600 (A)	49	1.9	135	4.0	30	11.6	36.2
Oct 8, 2004	205 (F)	32	1.5	135	4.0	23	na	na
Jan 5, 2005	133 (F)	43	2.1	141	4.7	21	10.1	30.4
Apr 28, 2005	167 (F)	23	1.1	140	4.4	24	13.9*	42.7*
Nov 7, 2005	203 (F)	26	1.2	145	4.3	26	13.2*	38.3*

* Received no exogenous erythropoietin (Epogen, Procrit, or darbepoetin)

WF = white female, DM = diabetes mellitus, BUN = blood urea nitrogen, SCr = serum creatinine, Na = sodium, K = potassium, CO_2 = carbon dioxide, Hb = hemoglobin, Hct = hematocrit, F = fasting, A = accucheck, na = not available.

Adapted from Mandal AK, Hiebert LM. *Clin Nephrol* 2008;69:169-78 with permission from Dustri-Verlag, Munich, Germany.

Table 7. Serial serum chemistry during and after ARB therapy in 67AAF with long history of DM

Date 2001-2006	Glucose (F) mg/dL	BUN mg/dL	SCr mg/dL	Na* mEq/L	K* mEq/L	CO_2 mEq/L
Jan 5, 2001	151	35	2.6	137	3.7	30
Mar 1, 2001	Irbesartan & diuretic therapy started.					
Jan 29, 2002	800	86	5.8	134	3.3	35
Hospital admission, irbesartan & diuretics discontinued, normal saline infusion started.						
Jan 30, 2002	288	91	5.6	132	3.3	34
Jan 31, 2002	111	73	4.8	137	3.6	34
Feb 2, 2002	101	52	4.2	136	4.9	27
Discharged from hospital, irbesartan & diuretics reinstituted in office.						
Feb 11, 2002	95	69	4.4	139	5.0	27
Irbesartan & diuretics discontinued in office.						
Mar 11. 2002	109	36	2.8	136	4.7	26
May 7, 2002	111	44	2.9	139	4.0	31
Apr 14, 2003	236	35	2.8	138	4.2	34
Nov 17, 2003	139	37	2.7	141	3.9	27
Feb 6, 2006	208	30	3.1	142	4.2	30

ARB = angiotensin receptor blockers, AAF = African-American female, DM = diabetes mellitus, F = fasting, BUN = blood urea nitrogen, SCr = serum creatinine, Na = sodium, K = potassium, CO_2 = carbon dioxide.

Adapted from Mandal AK, Hiebert LM. Clin Nephrol 2008;69:169-78 with permission from Dustri-Verlag, Munich, Germany.

Table 8. Serial laboratory studies in 59 AAM with long history of DM

Date *2005*	*Glucose (F)* *mg/dL*	*BUN* *mg/dL*	*SCr* *mg/dL*	*Na** *mEq/L*	*K** *mEq/L*	*CO_2* *mEq/L*
Aug 18	302	76	7.4	126	5.9	15
Hospital admission: Lisinopril discontinued						
Aug 19	274	80	8.2	127	5.0	17*
Normal saline with 3 ampoules of sodium bicarbonate infusion started						
Aug 20	249	68	2.2	133	5.6	18
	196	22	0.8	139	4.2	32
	186	10	0.8	140	3.8	33
Discharged from hospital.						

AAM = African-American male, DM = diabetes mellitus, F = fasting, BUN = blood urea nitrogen, SCr = serum creatinine, Na = sodium, K = potassium, CO_2 = carbon dioxide.
* pH 7.31, base excess -7.7.

Adapted from Mandal AK, Hiebert LM. Clin Nephrol 2008;69:169-78 with permission from Dustri-Verlag, Munich, Germany.

Table 9. Effect of fosinopril on proteinuria and renal function in 67AAF with 12-year history of DM

Date *1999-2006*	*24-g Proteinuria* *mg*	*24-h Creatinine Clearance* *ml/min*	*Serum Creatinine* *mg/dL*
Oct 17, 1999	160	125	0.8
Fosinopril 20 mg daily started			
Nov 9, 2000	88	90	0.9
Dec 8, 2002	142	81	1.0
Feb 18, 2004	5	55	1.1
Fosinopril discontinued. Referred for decreased Creatinine Clearance			
July 15, 2004	151	96	1.0
Jan 20, 2005	417	76	1.0
Apr 7, 2005	215	86	0.9
Jun 8, 2006	257	70	0.7
Dec 11, 2006	< 150	80	0.96

Adapted from Mandal AK, Hiebert LM. Clin Nephrol 2008;69:169-78 with permission from Dustri-Verlag, Munich, Germany

All these patients reversed their renal function to normal or baseline by discontinuation of ACEI/ARB and treatment with bicarbonate infusion, exogenous erythropoietic stimulating agent, and 9-alpha fluorocortisone (aldosterone analog) for hyperkalemia. With this management, metabolic acidosis is corrected, serum potassium becomes normal, and anemia improves. Rarely acute hemodialysis was required, and no patient progressed to ESRD. The author finds no shred of evidence of renal protection by ACEI or ARB drugs in diabetes.

Newer Development in Diabetes Therapy

Tradition plays the most important part in practice of medicine. Insulin is a proven therapy for diabetes and there is no substitute for that. These newer developments are informative but not recommended by the author.

1. DPP-4 inhibitors: These drugs inhibit an enzyme (DPP-4) that deactivates a protein (GLP-1) that keeps endogenous insulin circulating. The first of DPP-4 inhibitor is Januvia® 100 mg orally once daily is a commonly prescribed drug. Utility of this drug in satisfactory glycemic control is undetermined.

2. Incretin mimetics: These mimic the action of incretin hormones, which help the body make more insulin. They also slow down the rate of digestion so that glucose enters the circulation slowly. Incretin mimetics make one feel full in stomach longer, thus reducing intake of food frequently, hence reduce weight. Byetta• (exenatide) is an injectable medication that is used in combination with OHAs. It doesn't take the place of insulin.
3. Symlin• (pramlintide acetate) is an injectable medication and is used with insulin for tighter glucose control.

These newer gadgets are scientifically interesting, but their application in diabetes management is farfetched. Once again, a combination of long-acting and short-acting insulin along with prescribed diet remains the mainstay of therapy for established diabetes defined by postprandial glucose of ≥200 mg/dL (≥11.1 mmol/L) and permissive of a healthy life.

KEY POINTS

1. Sustained hyperglycemia ≥200 mg/dL (≥11.1 mmol/L) is the fundamental problem of DM.
2. Hyperglycemia is same and produces complications in identical fashion in both Type 1 and Type 2 diabetes.
3. Therefore, treat hyperglycemia and not treat Type 1 or Type 2 DM.
4. Simply lowering of glucose doesn't reduce oxidative stress. Glucose must be oxidized to reduce oxidative stress and thus prevent vascular damage.
5. Insulin does it all and is the cornerstone of therapy.
6. Always search for a cause of hyperglycemia, such as hydrochlorothiazide, beta blockers used to treat hypertension; also steroid therapy for treatment of chronic bronchitis or chronic obstructive pulmonary disease, and tacrolimus, an immunosuppressive therapy for transplantation.
7. Spare beta cell from exhaustion and death—severe diabetes due to continuous overstimulation by oral antidiabetic agents.
8. Beta-cell mass decrease with duration of the disease and could be a consequence of diabetes that, with further impairment of insulin secretion, contributes to progressive deterioration of glucose homeostasis.
9. Consider dialysis as an accident and not as a routine therapy for diabetes-related kidney disease by paying full attention to glycemic control.
10. Mellow down obsession to use ACEI/ARB drugs to reduce proteinuria and the risk of ESRD. It is evident that long-term use of these drugs increase the risk of ESRD.
11. There is nothing better in short of satisfactory glycemic control with insulin preparation and blood pressure control with antihypertensive drugs other than ACEI/ARB drugs.
12. Hyperlipidemia is secondary to uncontrolled hyperglycemia. Therefore, antilipidemic drug therapy in short of satisfactory glycemic control is ineffective in preventing complications.

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Diabetes and Sexual Dysfunction: Etiology, Pathology, and Treatment

Anil K Mandal

INTRODUCTION

Diabetes has a severe impact on sexual life in both men and women. There is abundant information on the effect of diabetes in reproductive activity in women, such as abnormal menstruation, abnormal pregnancy, miscarriage, difficult child birth, large babies, and fetal morbidity and mortality. On the other hand, information is meager on sexual activity of the women, such as sexual desire, arousal, and sexual satisfaction mainly due to slight or no dialogue in that area between the female patients and the health care providers. This is worse in underdeveloped and developing countries where sex is considered as a taboo, and it is a very sensitive area for discussion even by the doctors. Even in the developed countries, such as the United States of America or Canada, the women do not come forward to report their sexual problems to the doctors. According to a national survey, the MUSE Impotence Report, most men (64 percent) have never discussed their sex life with a physician. And most women (58 percent) mistakenly believe that their partners would be upset, if they took the initiative in arranging a doctor's appointment to discuss sexual dysfunction.

Finding very little information about the sexual function in both men and women, the author has started to bring up that area with his office-based patients. When asked, both men and women candidly speak about their sexual problems. It seems though that they were waiting for an opportunity to speak about their sexual problems to someone they can rely on.

Erectile dysfunction (ED) is very common among the men with diabetes. Most of them have uncontrolled diabetes with 2-hour postprandial glucose (2hPP) level in the range of 300 to 400 mg/dL (16.6 to 22.2 mmol/L). Some of them are treated with insulin; most are not, and their glycemic control is poor, which is partly due to noncompliance in diet therapy. However, there are other patients whose glucose control is fair or satisfactory, but they have already developed other complications, including ED, related to undetected or untreated hyperglycemia in the past. Up to 45 percent of the patients with diabetes have developed end stage renal disease (ESRD) and are currently treated with maintenance dialysis therapy.

When patients—men or women—develop ESRD and are treated with dialysis, most of them have lost their sexual desire as well as capability to perform sexual activity. A few people experience sexual desire and can perform sex. Manipulations that are available to improve sexual performance are not uniformly successful. Therefore, severe renal failure, such as warranting dialysis, has additional negative impact on sexual function over and above that caused by diabetes. The exact mechanism by which renal failure contributes to sexual dysfunction is not yet elucidated. Depression and anxiety associated with renal failure or dialysis may be contributing factors. Zinc deficiency was found to be a cause of ED in dialysis patients. But zinc replacement has only slight effect in restoring sexual function in dialysis patients.

ERECTILE DYSFUNCTION IN MEN

Erectile dysfunction (ED) is the inability to achieve or maintain an erection firm enough and long enough for sexual intercourse to satisfy partner. It is a common complaint in adult males, and its prevalence increases with age. In men, impotence may come and go at times. It may begin with erections that are less than firm before and then progress to those that are less firm and of shorter duration than before. Diabetes is a very common, if not the most common cause of ED. Up to 75 percent of men with diabetes have a lifetime risk of developing ED and 52 percent of men ages 40 to 70 years without diabetes have ED. Onset of ED occurs sooner in men with diabetes compared with men who do not have diabetes. Because the metabolic syndrome is a marker for diabetes, patients with ED and metabolic syndrome are at increased risk for diabetes. Therefore, it is prudent to state that ED and diabetes go hand in hand. The man will continue to have interest in sex and be able to have orgasms. It is thought that this process occurs in about half of all diabetic men and is caused by diabetic neuropathy. Impotence can be slowed down and treated, but actual tissue damage cannot be reversed. It is, therefore, very important to report symptoms early as opposed to later in the process to get the most effective treatment. ***Sometimes impotence is a flag of undiagnosed diabetes.*** It comes with the other classic signs of the diabetes. In these cases, it can usually be resolved with satisfactory control of glucose levels (less than 200 mg/dL or 11.1 mmol/L).

The exact mechanism of ED is not yet elucidated. However, the author's cell culture studies have shed some light in understanding complications of diabetes, including ED. These studies have shown that high glucose concentration in the culture plate (540 mg/dL or 30 mmol/L), as in the uncontrolled diabetic patients, causes severe damage to the vascular endothelial cells. These damaged endothelial cells shed off and may lead to complete occlusion of the microvascular apparatus of the penis as in kidneys, heart, or feet. Therefore, lack of blood flow through the penis during sexual excitement cannot make the penis turgid, which is required for complete penetration and satisfactory intercourse.

Typically, ED affects middle-aged or older diabetic males. In a survey of 541 diabetic men aged 20 to 59 years, the prevalence of ED was 6 percent for diabetic men age 20 to 24 years but 52 percent for those 55 to 59 years old or older, as shown in Figure 1.

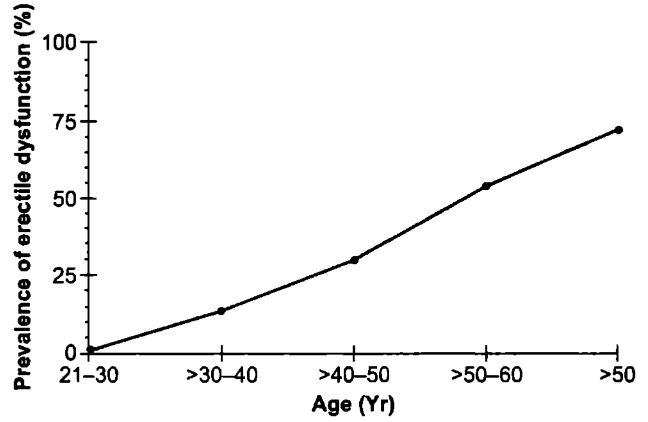
In another study ED prevalence was evaluated in 365 men age 21 years or older with duration of diabetes of 10 years. The prevalence was 1.1 percent in the 21-to-30-year-old group and 75 percent in those 60 years old or older (Fig. 1). In addition to increasing age and poor glycemic control, ED is also associated with smoking, obesity, low HDL, and other diabetic complications, such as neuropathy and retinopathy.

Overall Assessment of ED

There is a great deal of lack of information about ED in men and sexual dysfunction in women. This lack of information is mainly due to lack of communication between the patients and their providers. Also it is commonly believed that ED in diabetic subjects is due to neuropathy and microvascular disease, thereby discouraging providers to further investigate for other causes of ED.

In a study from Taiwan, HbA1c level, age, and duration of diabetes were found to be significant independent risk factors for ED among the younger group (age ≤60 years) and only age and duration of diabetes were found to be independent risk factors among the older group (>60 years). This study concluded that better glycemic control probably would reduce the prevalence of ED and its severity among the younger men with diabetes. However, age is an important determinant of ED beside diabetes among the older people.

ED is considered by other investigators as multifactorial, including endocrine, neurological, vascular, systemic disease, local penile disorders, psychogenic, and nutrition. Peripheral venous levels of testosterone, prolactin, follicle-



Klein R, Klein BEK, Lee KE, Moss SE, Cruikshanke KJ. Prevalence of self-reported erectile dysfunction in people with long-term IDDM, Diabetes care 1996:19:135–141 with permission

Figure 1: Relationship of age to the prevalence of erectile dysfunction in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (1990-1992)

stimulating hormone (FSH), luteinizing hormone (LH), thyroid-stimulating hormone (TSH), malondialdehyde, and HbA1c were obtained in control subjects and in diabetics with ED. Testosterone, prolactin, FSH, LH, and TSH were not different between the control and diabetics with ED, suggesting that these hormone levels have slight or no role in the pathogenesis of diabetic ED.

ED is increasingly considered as a surrogate marker of endothelial dysfunction as well as a sentinel predictor of new-onset microangiopathic events. Therefore, diagnosing ED in diabetes may herald the onset of other vascular disorders, such as peripheral vascular disease, transient ischemic attacks or stroke, retinopathy, and proteinuria.

DM may affect male reproductive function at multiple levels as a result of its effects on the endocrine control of spermatogenesis, spermatogenesis itself, or by impairing penile erection and ejaculation. All those sexual dysfunction in and of itself may contribute to subfertility in men. Semen samples from nondiabetic control and diabetic group were compared. The results are shown in Table 1.

As expected, mean HbA1c is significantly higher in the diabetic than control group. Abstinence time did not differ between the groups. Semen volume in diabetic men was significantly less than that of nondiabetic control. No significant differences were observed in sperm concentration, total sperm output, percentage motility, or percentage of morphologically normal sperm. However, percentage of damaged sperm as determined by fragmented sperm nucleus DNA was significantly higher in diabetic subjects compared with that in nondiabetic controls.

Most patients with diabetes will not volunteer information about their sexual function, as stated before. Thus, it is very important for the doctor to inquire about ED in all men with diabetes. One should not immediately conclude that ED is caused by diabetic neuropathy or vasculopathy.

Review of medications is very important as many blood-pressure-lowering drugs cause ED. Notable among them are clonidine, atenolol, Aldomet, and hydrochlorothiazide. For example, a 52-year white male is regularly followed by the author for high blood pressure. He did not complain of sexual problem. He receives amlodipine, hydrochlorothiazide, and enalapril. When asked, he expressed frustration about lack of sexual desire and inability to obtain erection. His blood pressure is not fully under control. He blames the medicines that make him sleepy; therefore, he does not feel the desire to perform sex. History of alcohol and drug abuse if any is essential. Alcoholics often develop ED. It is important to obtain serum testosterone and prolactin levels. Free testosterone is more reliable than total testosterone. Referral to an endocrinologist is appropriate for those with low total testosterone and hyperprolactinemia. ***Depression is particularly common in diabetics because they feel that their life is doomed. Because of diabetes, which requires life-long therapy, depression can be an important factor in the development of ED.***

In a study from Oxford, United Kingdom, 269 men with variable ED were studied in a clinic in

Table 1. Comparison of age, HbA1c and semen profiles from control and diabetic men

		Group		
	Control (n=29)	*Diabetic (n=27)*	*P-value*	*WHO[a] normal*
Age (years)[b]	32.7 ± 0.7	34.0 ± 2.0	0.52	
[b]HbA1c (%)[b]	5.3 ± 0.1	8.2 ±0.2	<0.0001	
Semen volume (ml)[b]	3.3 ± 0.2	2.6 ± 0.3	<0.05	2–4
Semen concentration (10^6 ml^{-1})[c]	52 [28–100]	64 [30–151]	0.22	>20
Total sperm output (10^6)[c]	173 [89–338]	198 [99–450]	0.84	–
Motility (%)[b]	47.3 ± 2.8	46.0 ± 4.2	0.79	>50
Normal Morphology (%)[b]	11.7 ± 0.8	11.1 ± 0.6	0.56	>14

[a] World Health Organization normal reference values (WHO, 1999).

[b] Values expressed as mean ± SEM.

[c] Values expressed as median [inter-quartile range].

Adapted from Agbaje IM, et al. Human Reproduction 2007;22:1871-77 by permission.

Colombo, Sri Lanka. All men here diabetic; 185 had variable degree of ED, while 84 had severe ED. After excluding 84 men with severe ED, a multivariate analysis found strongest association with ED in order: (1) premature ejaculation (OR=4.41); (2) reduced libido (OR=4.38); (3) lower income (OR=2.16); (4) advancing age (OR=2.06); (5) duration of diabetes (OR=1.48) (Table 2). A multivariate logistic regression analysis also showed hypertension as an independent predictor in addition to those in Table 2.

Absence of morning erections was associated with ED (P<0.0001) and advancing age (P<0.001), and the association with ED persisted after controlling for age (P<0.001). In addition, ED was univariately associated with lower educational level, presence of hypertension, and alcohol intake. The authors concluded that ED was strongly associated with premature ejaculation and reduced libido.

Infertility in Men

Reversible infertility in diabetic men with ED is not uncommon. A 32-year-old Chinese man with insulin-dependent diabetes developed ED and infertility with total azoospermia. The azoospermia was reversed following improved glucose control with soluble insulin three times daily. With reversal of azoospermia, his wife conceived five months later.

Table 2. Factors predicting erectile dysfunction (ED) (any degree of ED compared with normal erectile function in multivariate analysis)

Variable	*Significance P values*	*Odds ratio (exponent of beta)*	*95% confidence interval*
Presence of premature ejaculation	<0.001	4.41	(2.08 – 9.39)
Presence of reduced libido	0.012	4.38	(1.39 – 13.82)
Lower monthly income	0.002	2.16	1.32 – 3.52)
Age (10-year increment)	<0.001	2.06	1.44 – 2.95)
Duration of diabetes (5-year increment0	0.012	1.48	1.09 – 2.01)

Adapted from Malavige et al. J Sex Med (2008; 5: 2125-2136) with permission.

Management of ED

General Considerations

There are many modalities of therapy for ED, but no therapy except glycemic control is specific for diabetes. However, there are no prospective studies done that demonstrate that tight glycemic control reverses ED. Since glycemic control can improve endothelial function, as already stated, it is imperative to maintain satisfactory glycemic control with insulin giving a hope to restore some amount of erectile function. Other modalities in short of glycemic control are nonspecific and unpredictable. Nevertheless, if the diabetic patient with ED has also high blood pressure and is taking medication to lower blood pressure, it is advisable to substitute certain medications, as already stated, with other medication to control blood pressure. Those medications will further aggravate ED. Similarly, avoid drinking alcohol or taking sleeping medications, which will inhibit sexual desire and impair the ability to achieve sexual intercourse. Start an exercise program and healthy diet to lose weight, thereby make yourself attractive, give up smoking to make yourself look good, and start working to improve your relationship. It is amazing how sex life improves once you start to get the love and intimacy back in the relationship. The men should know that most females reach orgasm not with penis in vagina thrusting. Most females reach orgasm with touching, petting, fondling, fingering, oral-genital stimulation, and maybe a vibrator. Suddenly this takes all the pressure off having a humongous erection to be a good lover.

Maneuvers to Improve Erectile Function

Some psychological reasons may be stress, fear of sexually transmitted diseases, unplanned pregnancy, guilt or fear of discovery of performance anxiety. Reduce fear, anxiety, or stress with psychiatry counseling. Oral PDE5 inhibitors, such as Viagra, is most commonly prescribed drug to treat ED. The results are conflicting. Furthermore, side effects can be serious, especially for those who are taking nitrates for chest pain. A bad relationship or a big argument might result in erectile difficulty. Also, it may simply happen because a male is getting older. The temptation is to go to a doctor for a prescription of Viagra. Before taking that route, start on exercise program and healthy diet to lose weight, give up smoking, and start working to improve your relationship. Sex life improves once you start to get the love and intimacy back into the relationship. Temptation is high that Viagra or a similar drug will help you to do the sex but remember, if you are experiencing low or no sex drive and have reduced libido, these drugs will not help. Also, men with ED, please remember the following:

> *"...most females reach orgasm not with penis in vagina thrusting. Most females reach orgasm with touching, petting, fondling, fingering, oral-genital stimulation and maybe a vibrator. Suddenly this takes all the pressure off having a humongous erection to be a good lover.*
>
> *Do talk about this with your partner before embarking on a Viagra trip. If you have not had intercourse for a period of time, your partner may have accepted the fact that sex is over and done with. If the relationship is not great, your partner may be glad that's done with. If you were a lousy lover before, now you will still be a lousy lover with an erection. Your partner may feel pressured to have sexual intercourse, fearing that if she does not, you will go out and find another receptive partner. She may also resort to faking pleasure — this may harm the trust level in the relationship. Talk about it."*

Intracavernosal administration of PGE1 is effective. Both partners have experienced sexual satisfaction after PGE1 injection. However, the drop out rate of such therapy is high. Vacuum constrictor devices have enjoyed some popularity. Vacuum promotes arterial inflow and occlusive rings inhibit venous outflow from corpora cavernosa. The problem with vacuum device is inability to ejaculate because the occlusive ring that prevents venous drainage also compresses penile urethra and prevents ejaculation. It should be noted that women enjoy seeing ejaculation and feeling the wetness of the ejaculation. In short of ejaculation, sexual intercourse may not be gratifying to the women. If noninvasive or minimally invasive treatments are not effective, surgical prosthesis should be considered. The inflatable prostheses are more physiological, but there is small but significant incidence of mechanical failure. Consultation with an urologist may be helpful when conservative measures, including glycemic control with insulin, have failed to restore sexual activity.

SEXUAL LIFE IN DIABETIC WOMEN

Anatomy of Sexual Activity in Females

It is important to examine the anatomy of female sexual organs that will facilitate understanding of the sexual activity in healthy females and the derangements that may occur in diabetic females. Blood flow to the vagina is via the internal pudendal, perineal, and posterior labial arteries, while blood flow to clitoris is supplied by the dorsal and cavernosal arteries.

During arousal, the perivaginal tissues become vasocongested and vaginal transudation occurs in preparation for coitus. Prior to coitus, the uterus and cervix move upwards as the upper two thirds of the vagina expand in a ballooning effect. Clitoral tumescence occurs, and the glans clitoris protrudes, enhancing sensitivity during stimulation. Reduction in vaginal and clitoral blood supply, as can happen due to diabetic vasculopathy, may result in reduced vaginal lubrication and painful intercourse called dyspareunia. Further, reduced estrogen supply in menopausal women causes atrophic changes in vaginal epithelium with further reduction of lubrication and more painful intercourse leading to complete abandonment of penetration and sexual intercourse. Diabetic neuropathy may result in loss of clitoral sensation and no feeling for excitement or arousal during intercourse. Therefore, it seems likely that blood flow to the genitalia in women is as important as it is in men for overall sexual satisfaction.

Although sexual dysfunction is more common in diabetic women than control subjects, but no consistency is found with regard to sexual dysfunction among the reports about the risk factors or association with other complications of diabetes. After review of the literature, the author has raised a serious question if sexual life in diabetic women is affected by hyperglycemia and whether glycemic control can improve sexual function in diabetic women. To that effect, a univariate analysis of diabetic women with sexual dysfunction revealed a positive association between female sexual dysfunction and age, marital status, menopause, microvasculopathy, and depression. However, in a multivariate analysis, only ***depression and marital status*** were significant predictors of female sexual dysfunction.

Other studies concur with the above findings, indicating that sexual dysfunction in diabetic women is mainly of psychogenic origin. Feeling of loneliness and isolation are common among diabetic women with lack of partner understanding being seen as a contributory factor. It is important for the women as well as men with sexual dysfunction to know the following facts:

> *For 80 percent of the women who seek Sex Therapy, the presenting complaint is Low Sex Drive (LSD) or Inhibited Sexual Desire (ISD.) It used to be considered a female "problem" but now almost as many men as women complain of low sex drive. Couples used to have sex on average of 2.2 times a week. Today, if they are lucky, once a week is the norm.*

There can be many reasons. Professional therapists will assess whether the decreased sex drive is the result of:

1. DINTS - Double Income, No Time for Sex. With both partners working, the demands of children and aging parents, finances, job insecurity, many couples would rather just sleep than have a romp in the sack.
2. Sex is boring, partner may be inconsiderate or unresponsive.
3. Unresolved anger, resentment and hostility in the relationship. If... she feels that she is doing the lion's share of child care and housework, she is unlikely to be a sex kitten in bed. On the other hand if she pranged the car and blew the budget, he may find it difficult to become aroused and have sex.
4. If they have never established "clues", subtle little hints that "tonight's the night," if she feels like a slut for indicating that she is horny, or if he feels like an oversexed pervert implying that sex would be fun on Sunday morning, then they will both miss out.
5. If either is withholding sex to punish the other for some perceived injustice such as an affair.
6. Fear of an unplanned pregnancy or sexually transmitted disease such as warts or herpes. Or fear that the kids will barge in. Fear that he will hurt her during or after a pregnancy.
7. Guilt, if either has been involved in an outside relationship.
8. Sometimes one partner is simply turned off by sex.
9. Depression or anxiety.
10. After the birth of a baby, her sex drive does not come back, or he was so traumatized by pregnancy and delivery that he just does not want to touch his partner.

11. They love their partner, love hugging as long as it does not result in that "copulatory gaze" and the feelings of rejection if it is not returned.
12. Medications such as antidepressants, sedatives, high blood pressure medication, conditions such as diabetes, stroke, heart condition or Spinal Cord Injury.
13. Male or female sexual abuse, either past or present.
14. One partner may be turned off if their partner has gained a great deal of weight or has poor personal hygiene, does not shower or brush their teeth, etc.
15. Your hormone levels may be changing. You can get your doctor to check this.

All of these problems may be resolved with help from a professional. So, don't throw in the towel. Your sex life is like any other skill—work at it and it may get better. Counseling and learning better communication skills will help.

Hopefully, these facts will help to leave behind adversities in the relationship between a man and woman and work toward developing a congenial relationship.

It is true that some women with diabetes experience decreased sex drive or the ability to achieve orgasm. Like other complications of diabetes, sexual dysfunction is a slow and progressive pattern. Diabetic women have a predisposition to chronic vaginal infections, which may also interfere with normal sexual pleasures. Self-esteem is low among diabetic women. They feel that their bodies are less sexually attractive than nondiabetic women. Controlling weight will enhance self-esteem and body image.

In summary, reports on sexual dysfunction among diabetic women provide very conflicting results with no consistent pattern. Symptoms of sexual dysfunction include reduced libido, lack of vaginal lubrication, and, consequently, painful sexual intercourse. However, no solid evidence exists with regard to relationship between these symptoms and uncontrolled hyperglycemia. Similarly, very little evidence exists that glycemic control will improve these symptoms. However, some evidence exists as to depression, marital status, and lack of understanding by the partners, which might be contributing more to sexual dysfunction than uncontrolled hyperglycemia. This scenario coupled with numerous interventions available for male sexual disorders influences neglect of female sexual dysfunction. Finally, further investigations, especially the psychological aspect of diabetic women, are essential to elucidate pathogenesis of female sexual dysfunction and find effective treatment for amelioration. Until further developments happen, satisfactory glycemic control with insulin remains a mainstay of therapy for sexual dysfunction in diabetic women as it is in men.

KEY POINTS

1. Erectile dysfunction (ED) is very common among the men with diabetes.
2. Age is an important determinant of ED. Prevalence of ED increases with age without or with diabetes.
3. Onset of ED occurs sooner in men with diabetes compared with men who do not have diabetes.
4. The exact mechanism of ED is not yet elucidated, but it appears to be due to neuropathy and vascular endothelial damage from uncontrolled hyperglycemia.
5. Premature ejaculation, reduced libido, low income, duration of diabetes, and hypertension are important predictors for ED.
6. There is no specific therapy for ED. Good glycemic control may improve erectile function.
7. In ischemic heart disease, improving blood flow to heart with use of nitroglycerine tablet or spray or coronary artery bypass graft may improve erectile function and help in achieving sexual intercourse.
8. In diabetic women, information about sexual dysfunction is meager and mostly unfounded.
9. Depression and problem with marital status came out as strong predictors of sexual dysfunction in diabetic women.
10. Nevertheless, lack of vaginal lubrication, making penetration of distended penis painful, and low sexual desire are important determining factors for sexual dysfunction in diabetic women.
11. There is no established data to indicate that good glycemic control will improve sexual function in diabetic women.

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14

Diabetes: What does High Glucose do to Body Function?

Anil K Mandal

Glucose levels in a subject who is not diabetic are:

- After overnight fasting is less than 126 mg/dL (7 mmol/L), better is less than 100 mg/dL (5.5 mmol/L)
- Two hours after normal breakfast or lunch (not tea and toast or salad and soup) less than 200 mg/dL (11.1 mmol/L); better is less than 140 mg/dL (7.7 mmol/L).

On the other hand, in subjects with established diabetes but untreated: overnight, fasting glucose can be over 200 mg/dL (11 mmol/L) and two hours after breakfast or lunch can go as high as 400 or 500 mg/dL (22.2 or 27.7 mmol/L).

In borderline cases, for example fasting, glucose levels may range from 120 to 125 mg/dL (6.6 to 6.9 mmol/L) and two hours, glucose levels after a meal may range from 160 to 180 mg/dL (8.8 to 10 mmol/L). In such cases, a two-hour glucose tolerance test is recommended. This test is done in a clinical laboratory. A blood sample is drawn in the fasting state. Then 70 g of glucose dissolved in 300 ml of water is given to the person to drink. Thereafter, blood samples are drawn after one and two hours of the ingestion of glucose. The results of the two-hour glucose tolerance test are in Table 1.

People with established diabetes whose blood glucose level remains elevated above 200 mg/dL (11.1 mmol/L) without treatment with insulin can develop complications acutely or in a protracted (chronic) fashion. While acute complications reverse with intensive therapy, protracted or chronic complications do not necessarily reverse to normal even with intensive therapy.

The two serious acute complications are diabetic ketoacidosis and diabetic coma. High uncontrolled sugar level is associated with frequent urination accompanied by excessive loss of body water (dehydration). Details will be found in Chapter One. Lack of insulin, which results in very high blood sugar level even up to 1000 to 1500 mg/dL (55.5 to 83.3 mmol/L) is associated with elevated levels of growth hormone, adrenaline, and cortisol. All these secondary hormones lead to breakdown of fat and increased release of fatty acids from liver. The byproducts of these fatty acids are acetoacetic acid, which lower blood pH and make the person acidotic. As a result of dehydration, kidney function is decreased giving rise to acute kidney failure.

Further, very high blood glucose levels—for instance, 800 mg/dL (44.4 mmol/L) or 1000 mg/dL (55.5 mmol/L) —increase the osmotic pressure in the blood and produce an imbalanced state of the water content between intracellular space and extracellular space, which is the

Table 1. Results of two-hour glucose tolerance test in fasting and glucose-induced state

	Glucose Tolerance		*Established*
	Normal	*Impaired*	*Diabetes*
Fasting plasma glucose (mg/dL/mmol/L)	70–99/3.8–5.5	110–125 6.1-6.9	≥126/7
2 hours after glucose load (mg/dL/mmol/L)	≤140/7.7	>140 <200 >7.7 <11.1	≥200/11.1

circulating blood space. Intracellular fluid spaces are brain, liver, heart, and kidney. When the osmotic force in the circulating system increases, water moves away from the above organs into the circulating system to make the balance of the water content between the two spaces. The result is drying of the cells. When brain cells dry up, brain shrinks and herniates, resulting in coma. Liver cells become dry and lead to necrosis with elevated liver enzymes; similarly, heart cells undergo necrosis and lead to heart failure, and kidney cells necrosis leads to acute kidney failure. Therefore, a diabetic patient with very high glucose levels, if not treated quickly with insulin infusion and fluid therapy, can develop catastrophic events associated with high death rate.

Chronic or protracted complications due to untreated high glucose levels in the blood not high enough to cause acute complications as stated above but can cause one or more of the following complications: These complications are not in any order:

- Retinopathy leading to partial or complete blindness
- Nephropathy leading to progressive renal failure and dialysis
- Neuropathy leading to urinary retention and foot ulcer
- Sexual dysfunction
- Gangrene of foot or toes leading to amputation
- Coronary heart disease leading to myocardial infarction or heart attack
- Neurogenic bladder leading to recurrent urinary tract infection
- Gastroparesis and paralytic ileus leading to recurrent vomiting, loss of nutrition, and cachexia.

When patients present to a doctor's office with one complication, such as foot ulcer or gangrene, they usually have one or more of the other complications. These complications are due to microvascular and macrovascular lesions as are generally stated. An important question is about the threshold of glucose level above which complications are likely to develop and below which complications are unlikely to develop. Even more important question is why glucose particles in the normal range (80 to 100 mg/dL or 4.4 to 5.5 mmol/L) do not produce any complications but do so when it increases to 200 mg/dL (11 mmol/L) or more. What difference does it make for increase in range of the same glucose particles? Therefore, a big question is: are glucose particles same or different in someone who is not diabetic versus who is diabetic?

Author's research involving cell culture studies attests to the fact that elevated glucose level, in and of itself, even of similar particles, has something to do with the complications. In the laboratories of the author in Dayton, Ohio, and his collaborator Dr. Linda Hiebert in Saskatoon, Canada, porcine vascular endothelial cells were cultured for growth of the cells and then treated with normal concentration of glucose (90 mg/dL or 5 mmol/L) or high concentration of glucose (540 mg/dL or 30 mmol/L) for a period of two days, six days, or ten days. Additional cultured cells were treated with glucose of the same concentrations as above and insulin or with glucose, insulin, and heparin.

Why are vascular endothelial cells chosen and not other cell types? There is good evidence in the literature that vascular endothelial cells are most vulnerable to injury by high blood glucose levels (hyperglycemia). High glucose levels bathe all the cells in the body. But why does damage occur in some cell types in diabetes? The answer is that most cells are able to reduce the transport of glucose inside the cells when they are exposed to high glucose levels, so that their internal glucose concentration remains constant. In contrast, the cells damaged by high glucose concentration are those that cannot retard transport of glucose inside the cells. Thus, in diabetes, endothelial cells and mesangial cells cannot reduce transport of glucose inside the cells in the state of high glucose levels in the blood. In essence, defect in membrane transport of endothelial cells permits excessive amount of glucose to enter inside the cells when glucose level is high. Therefore, complications that develop in diabetes must involve mechanisms of excessive amount of glucose inside the cells, rather than outside of the endothelial cells.

In our cell culture studies, we have demonstrated crystalline structures that are presumably glucose in severely damaged cells, as shown in Figures 1 and 2. Even endothelial cells that were revived by insulin treatment reveal telltale evidence of crystalline structures presumably glucose, as shown in Figure 3.

Many hypotheses or pathways were proposed to explain high glucose-induced cellular damage that is set in and perpetuates damage to the various organs and gives rise to appearance of clinically evident disease,

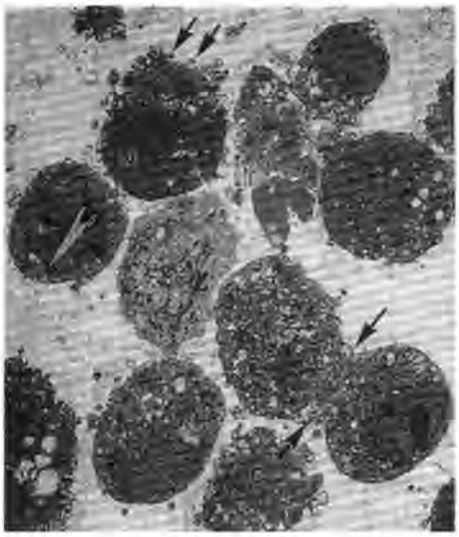

Figure 1: Crystalline structures, presumably glucose, in severely damaged cells

Crystalline structures between dark arrow heads.
C = connection between damaged cells.
N = damaged nucleus.
Source: Mandal AK and Hiebert LM. Renal protection in diabetes: is it affected by glucose control or inhibition of the renin-angiotensin pathway? Clinical Nephrology 2008;69(3):169-78, Figure 1.

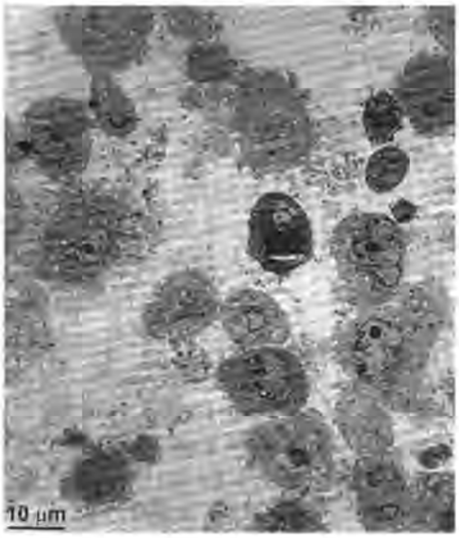

Figure 2: Crystalline structures, presumably glucose, in severely damaged cells

Note crystalline structure in an isolated cell in the open area.
Source: Mandal AK and Hiebert LM. Renal protection in diabetes: is it affected by glucose control or inhibition of the renin-angiotension pathway? Clinical Nephrology 2008;69(3):169-78, Figure 1.

such as retinopathy, heart attack, foot ulcer, gangrene, or kidney failure. None of the pathways thus far advanced explains damage to all the organs in a unified fashion. Author has proposed a better unified theory, which is ischemia (markedly reduced blood flow), which explains damage to all the organs. Reduced blood flow in an indolent fashion does not cause necrosis but causes atrophy. This is evident in heart as myocardial fibrosis and cardiomyopathy or atrophic tubules and interstitial fibrosis in kidneys. Progressive kidney failure is more due to loss of tubules and interstitial fibrosis rather than glomerular sclerosis.

Inability to achieve penile erection is clearly due to lack of blood flow through the penile microvasculature. Reduced blood flow can be associated with increased vascular permeability, resulting in exudation of plasma proteins in the free surface outside of the vessels. This is best seen as hemorrhages and exudates in the retina of eyes and as protein leak from kidney glomeruli in diabetes. Reduction of high blood glucose to normal or near normal level with insulin results in mitigation of endothelial damage and repair, consequently, partial or complete recovery of organ function. Like this author, other authors have considered that diabetes-specific microvascular disease in the eyes (retina), kidney glomeruli, and *vasa nervorum* (small vessels surrounding nerves in feet and penis) has similar pathophysiologic features.

Still, other authors found from experiments in rats that protein leak in urine or proteinuria is due to excessive filtration pressure of the kidney glomeruli caused by high glucose level. Further, these authors determined that this excessive filtration pressure causes glomerular sclerosis and kidney failure. Based on this theory, these authors proposed that angiotensin-converting enzyme inhibitors and, subsequently, angiotensin receptor blockers group of drugs can reduce filtration pressure of kidney glomeruli and in so doing reduce the risk of glomerular sclerosis and kidney failure.

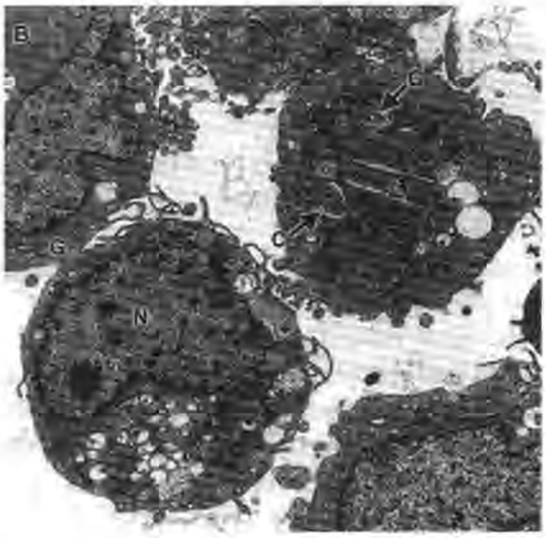

Figure 3: Evidence of crystalline structures, presumably glucose, in endothelial cells revived by insulin treatment

Crystalline structures between white arrows.
N = normal nucleus.
Source: Mandal AK and Hiebert LM. Renal protection in diabetes: is it affected by glucose control or inhibition of the renin-angiotensin pathway? Clinical Nephrology 2008;69(3):169-78, Figure 2.

The greatest pitfall of this theory is why will high glucose levels cause damage to the kidneys in a way that is entirely different from its adverse effect on other organs.

Fundamentally, the bad effects of high glucose level will be felt uniformly in all organs as considered by the author of this book and other authors. Once again, the uniformly bad effect of high blood glucose is necrosis of vascular endothelial cells, sloughing off of these cells into the capillary lumina forming microthrombi along with cholesterol and platelet deposits and resulting in occlusion of capillaries with slight or no blood flow to the organs. Hyperglycemia (high glucose level) was induced in rats to find changes in kidney glomeruli in the past. Very subtle changes were found in the kidney glomeruli; no changes were found in the tubules and interstitium. Rats did not develop kidney failure. This pitfall is the worst of the utility of experimental studies in live animals in trying to elucidate the pathogenesis of the complications associated with diabetes in humans. On the other hand, cell culture experiments done by the author and the collaborating authors have paved the way in better understanding of the pathogenesis of diabetic complications and how will these complications be adequately prevented.

The exact mechanisms of injury to the vascular endothelial cells and tubular epithelial cells caused by high glucose levels are not yet fully elucidated. Some authors have shown that high blood glucose levels increase oxidative stress and increase the production of reactive oxygen species.

We have considered that toxic oxygen radicals may be involved in ischemic injury to the organs and we designed an experiment to determine that. Glutathione is an important enzyme for oxidative stress. Therefore, by inhibiting glutathione, oxidative injury may increase. We treated vascular endothelial cells with a potent glutathione inhibitor for two days and six days. After six days of treatment, endothelial cells had undergone severe necrosis beyond recognition. Thus, this experiment suggests that deficiency of glutathione may be an important mechanism of diabetic microvascular complications.

Our cell culture studies have helped us to undermine the mechanism of protection against high glucose-induced cellular damage. We treated the cultured endothelial cells with insulin and with insulin and heparin in the presence of high glucose level in the culture medium. We noted slight or no morphological damage to cells, as shown in Figure 4. We have postulated that insulin reduces oxidative stress. Heparin seems to be additive to insulin in that effect. This had been shown by my collaborating author.

There is one mechanism by which heparin may synergize insulin. We have found that high glucose as well as insulin increases endothelin-1 production in the cultured endothelial cells. Heparin is a potent inhibitor of endothelin-1. Endothelin-1 is a potent vasoconstrictor and can aggravate ischemic injury to the endothelial cells. Therefore, by inhibiting endothelin-1 production, heparin may synergize insulin effect in protection against high glucose-induced cellular injury.

Overall, since hyperglycemia or high glucose level is the culprit of diabetic complications, lowering of

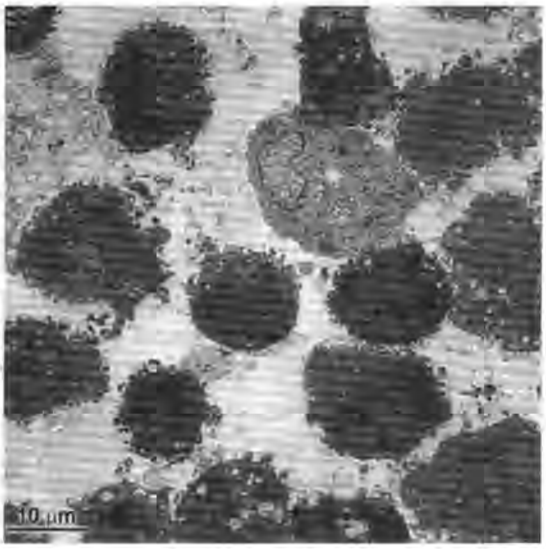

Figure 4: Slight or no morphological damage to cells

Source: Mandal AK and Hiebert LM. Renal protection in diabetes: is it affected by glucose control or inhibition of the renin-angiotensin pathway? Clinical Nephrology 2008;69(3):169-178, Figure 2.

high glucose level by therapy is the logical answer for prevention of its complications.

High blood glucose level can be lowered by oral antidiabetic agents, insulin injections, a combination of both, or dialysis against a glucose free bath. The latter was never put in practice except those who are on dialysis for end stage kidney failure. Preservation of renal function is of slight consequence in patients who already are on dialysis. It is evident in the literature that lowering of high blood glucose level can prevent diabetic complications. But no systematic studies were done to unequivocally show that simply lowering of high glucose level by oral antidiabetic agents, such as glyburide, metformin, or Januvia will prevent diabetic complications, as already stated. Occasional studies showed that use of metformin alone in Type Two diabetes reduced the risk of death or risk of myocardial infarction. The most important caveat of Type Two diabetes is that some of the patients in this type of trial may not have diabetes. Type One or Type Two was never defined appropriately, such as by two-hour postprandial glucose level or glucose tolerance test. Diabetes whose two-hour postprandial glucose is above 200 mg/dL (>11.1 mmol/L), oral antidiabetic agents can be used in addition to insulin to achieve better glucose control than either alone. However, the primary outcomes, such as microvascular complications, are not affected, despite improved glucose control. Two studies are cited to that effect.

1. 390 patients treated with insulin in the outpatient clinics of three hospitals for a period of 4.3 years received metformin (850 mg) or placebo (one to three times daily). The primary end point was an aggregate of microvascular and macrovascular morbidity and mortality, as separate aggregate scores. Metformin treatment prevented weight gain, improved glycemic control, and reduced insulin requirement but didn't improve the primary end points. Metformin did, however, reduce the risk of macrovascular disease after a follow-up period of 4.3 years.
2. In an unpublished study from Kolkata, India, by the author and Dr Aswini Patnaik, 312 patients with diabetes were treated with insulin, oral hypoglycemic agents, or combination of both. Paired fasting glucose, 2-hour postprandial glucose, and glomerular filtration rate as eGFR were obtained before and after 12-month period. Percentage decrease in glucose levels were greater in the group treated with insulin and oral hypoglycemic agents, but eGFR percentage change was significantly higher in insulin group than in other two groups.

In author's cell culture studies, when cells were treated with glucose and insulin, glucose measurement in culture plate showed slight or no change in concentration of glucose, although morphologically cells were intact. This finding suggests that insulin has a protective effect, which may be independent of simply lowering of glucose. Thus, combining clinical studies with the adjunct of cell culture studies, it is prudent to state that insulin is the cornerstone of therapy for prevention of cellular damage and hence appearance of clinical complications. There is no shred of evidence that simply by lowering of glucose levels with oral antidiabetic agents, including the new ones, prevention of diabetic complications can be accomplished.

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Nondiabetic Renal Disease in Patients with Type 2 Diabetes Mellitus

Jai Prakash

INTRODUCTION

Diabetes mellitus (DM) is fast becoming a world epidemic. Type 2 DM accounts for >90 percent of all cases of diabetes and its incidence is rapidly increasing particularly in developing countries. Diabetes specific renal disease (Diabetic nephropathy) develops in about one third of all people with Type 1 or Type 2 diabetes and it contributes to about 30 percent of end-stage renal disease (ESRD) in various countries. Although, patients with Type 2 DM often experience diabetic nephropathy (DN), they can also develop other renal diseases, pathologically unrelated to diabetes and known as nondiabetic renal disease (NDRD). In contrast to Type 1 DM, the incidence of NDRD is very high in Type 2 diabetic patients. Renal biopsy studies suggested that 25 to 50 percent of patients with Type 2 diabetes had glomerular lesions unrelated to or in addition to DN. DN can occur in absence of diabetic retinopathy (RP) in Type 2 DM. The presence of RP suggests the concurrence of DN, but does not exclude nondiabetic nephropathy (NDN). Clearly, renal biopsy is indicated in proteinuric Type 2 diabetic patients for precise diagnosis of diabetic vs. NDRD. Precise diagnosis of these various diseases has obvious prognostic and therapeutic implications. Appropriate treatment of NDRD is associated with good clinical outcome. This article will focus on clinical spectrum of NDRD in Type 2 DM and will address following issues:

1. Prevalence of NDRD
2. Clinical features of NDRD
3. Pathological lesions of NDRD
4. Renal-retinal relationship in Type 2 DM
5. Management and prognosis
6. Key points

PREVALENCE OF NDRD IN TYPE 2 DM

It is now accepted that clinical nephropathy (proteinuria) in Type 2 diabetic patients may be histologically associated with the development of diabetic glomerulopathy or NDRD or both. It has been reported that 12 to 80 percent of Type 2 diabetic patients with renal involvement show NDRD. The large variation reported in these studies may be due to selection bias because renal biopsies were performed in those with clinically atypical DN. In one kidney biopsy study, prevalence of NDRD among the Type 2 DM patients was 22 percent of European and 26.7 percent of Asian patients. Of 52 patients with overt proteinuria, 20 (38.5 percent) showed NDRD, while 32 (61.5 percent) patients exhibited DN. We had reported prevalence of NDRD in 43.7 percent of cases, while DN was diagnosed on biopsy in 13 (56.3 percent) proteinuric Type 2 diabetic patients. A retrospective analysis of kidney biopsy of Type 2 diabetic patients (n=233) reported NDRD in 124 (53.2 percent), pure diabetic glomerulosclerosis (DGS) in 64 (27.5 percent) and concurrent NDRD and DGS in 45 (19.3 percent) cases. The reported prevalence of NDN ranged from 25 to 45 percent in proteinuric Type 2 DM patients. Biopsy studies suggest that 25 to 50 percent of patients with Type 2 diabetes have glomerular lesions unrelated to or in addition to DN. It means that exact incidence of NDN is not known in Type 2 diabetic patients. However, NDRD in patients with Type 2 DM is highly prevalent (Table 1).

CLINICAL FEATURES OF NDRD IN TYPE 2 DM

DN is the most frequent (95 percent) cause of renal disease in patients with Type 1 DM, whereas NDN is rare, accounting for 2 to 3 percent of unselected diabetic patients with proteinuria. However, in Type 2 diabetic patients, persistent proteinuria and/or impaired renal function may be caused by a concurrent or an unrelated renal lesion namely nondiabetic-renal disease (NDRD). NDRD is a common feature in patients with Type 2 diabetes and has significant impact on prognosis and treatments which are different from DN. Renal biopsy is necessary to diagnose NDRD. However, it is generally agreed that renal biopsy cannot be used as a routine diagnostic test in Type 2 diabetic patients with proteinuria. Therefore, it is very important to determine the clinical predictive factors for NDRD in Type 2 diabetic patients. Factors, clinically associated with NDRD in patients with Type 2 DM remain unclear. The clues for NDRD in Type 2 diabetic patients are; (i) Nephrotic syndrome with normal renal function, (ii) Impaired renal function with no proteinuria, (iii) Absence of RP, (iv) Sudden deterioration of renal function, (v) Active urinary sediment, (vi) Gross or microscopic hematuria, (vii) Short duration of diabetes. Serra et al. reported that DGS was diagnosed in 17 (74 percent) patients without diabetic RP, in 18 (78 percent) patients with microhematuria and in 10 (67 percent) of these patients with microhematuria but without diabetic RP. Therefore, the presence of microhematuria and absence of diabetic RP do not predict nondiabetic renal involvement. We had reported that 50 percent of proteinuric Type 2 diabetic patients with typical DN on biopsy did not have diabetic RP.

Table 1. DN versus NDRD in type 2 DM: literature summary

Authors	*No. of Patients*	*NDRD*	*DN*
Hung F et al. (2007)	52	20(38.5%)	32(61.5%)
Pham TT et al. (2007)	233	124(53.2%)	109(46.8%)
Zhou J et al. (2007)	110	50(46%)	60(54%)
Parving HH et al. (1992)	35	08(23%)	27(77%)
Olsen S et al. (1966)	33	04(12%)	29(88%)
Prakash J et al. (2001)	**260**	**32(12.3%)**	**228(87.6%)**
Prakash J et al. (2007)	**23**	**10(43.7%)**	**13(56.3)**
†Christensen PK et al. (2000)	51	07(13%)	35(69%)
Serra A et al. (2002)	35	06(17%)	29(83%)
*Gambara V et al. (1993)	52	16(30.8%)	19(36.5%)
**Kveder K et al. (2001)	76	37(49%)	17(22%)

† Normal Histology (n=9); * DN + NDRD 17(32.7%); ** DN + NDRD 22(29%)

Causes of End-Stage Renal Disease (ESRD) in Type 2 DM

Diabetic ESRD related to Type 2 DM is the commonest cause of ESRD worldwide. However, several analyses have shown 20 to 30 percent of Type 2 diabetic patients with ESRD suffer from primary chronic renal disease such as polycystic kidney disease, analgesic nephropathy, glomerulonephritis and ischemic nephropathy (Table 2). Based on ultrasonographic examination and on renal biopsy finding, up to 20 percent of Type 2 DM were shown to have ischemic nephropathy secondary to atherosclerotic renal artery disease or cholesterol microembolism.

There is abundant evidence that the risk to develop proteinuria and renal failure is similar for patients with Type 1 or Type 2 diabetes (Figs 1 and 2). However, the incidence of ESRD in diabetic patients has increased dramatically in the past decades and majority of diabetic ESRD patients have Type 2 DM. The major reason for the apparent increase in the number of patients with Type 2 diabetes and ESRD is the progressive diminution of cardiac mortality in these patients so that such patients

Table 2. Causes of ESRD in patients with type 2 DM

1. Diabetic nephropathy
2. *Nondiabetic Renal Diseases (NDRD)
    a. Primary renal diseases
       Reflux nephropathy
       Polycystic renal disease
       Glomerulonephritis
    b. Ischemic nephropathy
    c. Bilateral renal artery stenosis
    d. Cholesterol embolism
    e. Benign nephrosclerosis
    f Irreversible ARF (X-ray contrast, sepsis)

* ESRD in Type 2 DM patient is related to NDRD in 40 to 60% of cases.

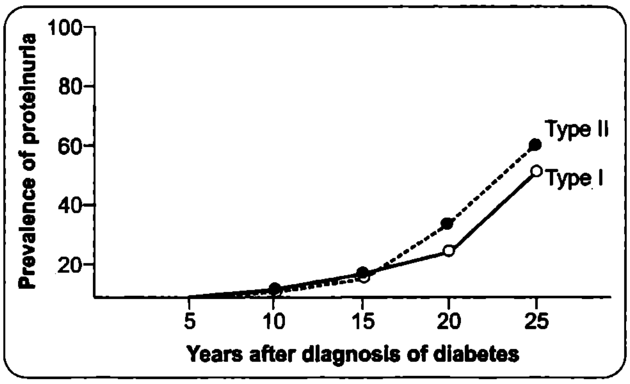

Figure 1: Cumulative prevalence of persistent proteinuria among patients with Type 1 or Type 2 DM according to the duration of diabetes

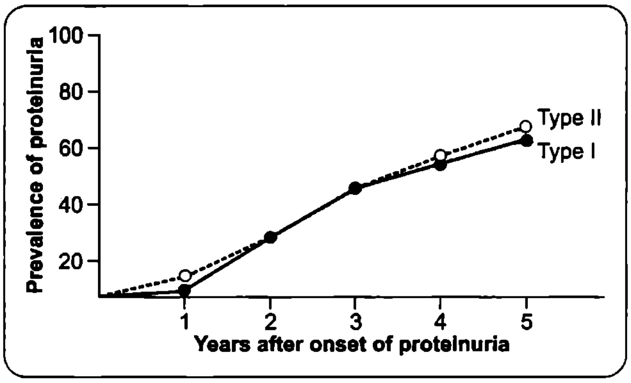

Figure 2: Cumulative prevalence of renal failure among patients with Type 1 or Type 2 DM, according to the duration of proteinuria

nowadays survive long enough to experience advanced nephropathy and ESRD. However, it is obvious that ESRD in Type 2 diabetic patients is not always associated with DN (Table 2). The high incidence of ESRD in patients with Type 2 diabetes is particularly a cause for concern, since medical rehabilitation, quality of life and survival are consistently worse in diabetic compared with nondiabetic dialysed patients.

HISTOLOGICAL LESIONS OF NDRD IN TYPE 2 DIABETIC PATIENTS

DN is the commonest cause of renal disease in diabetic patient. However, diabetic patients are not immune to the renal lesions other than DN. Indeed, it may be possible that the abnormal diabetic kidney is more susceptible to different types of glomerulonephritis. Renal lesions in Type 2 diabetes are much complex and differ in Type 2 and Type 1 diabetes. In contrast with Type 1 diabetes, the prevalence of NDRD in proteinuric Type 2 diabetic patients is very high. A wide spectrum of NDN including both glomerular and tubulointestinal lesions are reported in patients with Type 2 DM and their precise diagnosis requires histological examinations. Three patterns of histological lesions are described in these patients: (i) Isolated NDRD, (ii) Pure DGS and/or (iii) Concurrent NDRD and DGS known as combined diseases (CD). Renal biopsy in 23 cases revealed isolated DN in 13 (56.5 percent), NDN in 7 (30.4 percent) cases and 3 (13.1 percent) patients had combined disease (NDN and DGS). Pham et al. in their study reported that 53.2 percent, 27.5 percent and 19.3 percent of the patients had been diagnosed to have NDRD, pure DGS and concurrent NDRD and DGS, respectively. Retrospective biopsy studies of 236 (13 percent Type 1 and 87 percent Type 2) patients revealed isolated DN in 125 (53 percent), isolated NDRD 89 (38 percent) and NDRD superimposed on DN is 22 (9 percent) patients. Thus, prevalence of NDRD is remarkably frequent in diabetic patients. A wide spectrum of nondiabetic glomerulopathies can occur in patients with Type 2 DM including Membranous Glomerulonephritis, Focal Segmental glomerulosclerosis (FSGS), Minimal Change Nephropathy (MCN), RPGN, IgA nephropathy and amyloidosis. Membranous nephropathy (2), focal segmental sclerosis (2), and mesangiocapillary GN (1) were the nondiabetic glomerular diseases in our Type 2 diabetic patients. Among patients with nondiabetic tubulointerstitial lesions (n=5), three (60 percent) cases had chronic pyelonephritis and two (40 percent) patients showed ischemic interstitial nephritis. The tubulointerstitial and vascular changes are likely to be related not only to hyperglycemia, but also to aging, atherosclerosis and systemic hypertension, which often predate the onset of Type 2 diabetes. In patients with NDRD, the most common lesion was FSGS (21 percent), followed by minimal changes disease (15.3 percent) and in patients with concurrent NDRD and DGS, the most common lesions were IgA nephropathy, membranous glomerulonephritis and arterial/arteriolar nephrosclerosis seen in 15.6 percent, 13.3 percent and 13.3 percent of cases respectively.

In a biopsy study of 52 patients, 20 (38.5 percent) cases had NDRD and 32 (61.5 percent) patients showed DN (pure DGS 29; and NDRD along with DN in 3 cases). Idiopathic Membranous Glomerulonephropathy (MGN) has been reported in Type 2 proteinuric DM. Reported types of superimposed glomerular diseases on DN include IgA nephropathy, endocapillary proliferative glomerulonephritis, minimal change disease, membranoproliferative glomerulonephritis, rapidly progressive glomerulonephritis and cryoglobulenemic glomerulonephtiris. Concurrent DN and immune complex glomerulonephritis (postinfectious GN) had also been reported in Type 2 diabetic patients. Renal biopsy should be considered in these patients whenever clinical findings do not fit with the natural history of DN e.g., persistent hematuria; low complement levels or sudden deterioration of renal function. Short duration of diabetes and an absence of RP in a proteinuric Type 2 diabetic patient may predict NDRD.

Kidney Biopsy in Type 2 DM

The majority of patients whose history and clinical findings are compatible with diabetic kidney disease do not benefit from kidney biopsy, because the diagnosis is usually not altered. However, renal biopsy is helpful in diagnosis of certain treatable NDRDs in Type 2 diabetic patients. The clues for NDRD in Type 2 DM are:

i. Active urinary sediment
ii. Low complement levels
iii. Sudden deterioration of renal function
iv. Heavy proteinuria with normal renal function
v. Impaired renal function with normal and/or low grade of proteinuria
vi. Absence of RP
vii. Short duration of diabetes

However, criteria for renal biopsy in proteinuric Type 2 DM patients have not been defined. Usually, criteria for renal biopsy in Type 1 DM are used (duration of diabetes <five years, microhematuria, absence of diabetic RP, uncharacteristic changes in renal function or immunological abnormalities). DGS is the most commonly found renal lesions in Type 2 DM patients with proteinuria biopsied according to T1DM criteria even in the presence of microhematuria or absence of RP. Thus, these biopsy criteria are not useful in identifying patients with potentially treatable other renal lesions in Type 2 diabetic patients. Duration of diabetes and presence or absence of diabetic RP are not very helpful in distinguishing the type of nephropathy (DN vs NDRD) in Type 2 proteinuric diabetes patients. The author proposes that kidney biopsy should be performed in all proteinuric Type 2 diabetic patients for precise diagnosis of diabetic and NDRDs regardless of presence /or absence of diabetic RP.

RENAL-RETINAL RELATIONSHIP IN PROTEINURIC TYPE 2 DIABETES

Ninety to ninety-five percent of Type 1 diabetic patients with DN have RP. Forty percent to seventy-five percent of Type 2 diabetic patients with nephropathy have RP. From clinical point of view, the majority of patients with diabetic renal disease have RP. Hyperglycemia is the key initiating factor for development of microvascular complication of diabetes, and it takes years before complications such as RP or nephropathy (NP) develops. It has been shown that 47.5 percent of Type 2 diabetic patients with renal abnormalities (proteinuria and/or renal insufficiency) did not have diabetic RP, while majority of Type 1 diabetic patients with macroalbuminuria had some signs of RP. RP was detected significantly less frequently in Type 2 diabetic with DGS alone compared with Type 1 diabetes with DGS alone. Parving et al. noted that 40 percent of proteinuric Type 2 DM patients lacked diabetic RP. In another study there was no evidence of RP in one third of Type 2 diabetic patients with proven nephropathy. We observed four patients with biopsy proven DN who did not have evidence of diabetic RP. Biopsy study in 93 proteinuric patients with Type 2 DM without RP showed DN in 69 percent cases and 31 percent had either nondiabetic glomerulopathy (13 percent) or normal glomerular structure (18 percent). In another study renal biopsy in 76 Type 2 diabetic patients without RP revealed typical DN in 17 (22 percent), combined diabetic and nondiabetic glomerulopathy in 22 (29 percent) and 37 (49 percent) patients had only nondiabetic glomerulopathy. It should be pointed out that absence of RP cannot exclude the presence of DN because 50 to 70 percent of patients with DN do not have RP. Clearly DN can occur in absence of RP in Type 2 proteinuric diabetic patients Result of biopsy in 15 proteinuric Type 2 diabetic patients with RP revealed DN in 9 (60 percent) patients, isolated NDN in 3 (20 percent) and combined diabetic and NDN in 3 (20 percent) cases. In our previous publication 31 percent of patients with NDRD had background diabetic RP. Biopsy showed typical DN in 50 percent and NDN in 50 percent of our cases without RP. Gall et al. noted occurrence of diabetic and NDRD in equal number o their Type 2 diabetic patients without RP. These patterns reflect that chances of getting diabetic and NDRD are nearly equal in Type 2 diabetic patients in the absence of diabetic RP. Approximately, 20 to 40 percent of Type 2 diabetic patients with biopsy proven DN did not have evidence of diabetic RP. Huang et al. reported that patients with RP accounted for 43.75 percent of DN which is consistent with previous report. The renal-retinal relationship in Type 2 diabetic patient may not be helpful for clinical diagnosis of DN and lack of RP is a poor predictor of nondiabetic kidney disease in Type 2 diabetic patients. Therefore, presence or absence of diabetic RP did not prove to be significant enough in distinguishing DGS and NDN in Type 2 diabetic patients. Diabetic RP in proteinuric Type 2 diabetic patients may favor DN but does not exclude NDRDs. The renal biopsy is necessary for precise diagnosis of diabetic and nondiabetic renal lesions in proteinuric Type 2 diabetic patients even in the presence of diabetic RP.

MANAGEMENT OF NDRD IN TYPE 2 DIABETIC PATIENTS

It is well known that DN occurs in more than 95 percent of patients having Type 1 diabetes for more than 10 years, whereas NDN is rare, accounting for 2 to 3 percent of unselected Type 1 diabetic patients with proteinuria. Therefore, renal biopsy is not diagnostically useful in this disease setting. In the light of the high prevalence of NDRD, it is appropriate for performing renal biopsy in Type 2 diabetic patients with clinical suspicion of NDRD; especially with overt proteinuria with or without RP. The kidney biopsy is helpful in two ways: (i) It will differentiate diabetic from nondiabetic glomerulopathy and (ii) Knowledge of the underlying cause of proteinuria may play an important role in planning the correct treatment of these patients. Further, early diagnosis of NDRD is crucial as appropriate therapy could prolong renal survival in this patient population. The nature of specific therapy will depend on the nature of underlying NDRD (e.g., corticosteroid for minimal change disease/ or FSGS, combination of steroid and cytotoxic drugs for idiopathic membranous nephropathy, intensive immunosuppressive therapy for crescentic GN). Remission of nephrotic syndrome was observed with prolonged (four to six months) course of corticosteroid therapy in a Type 2 proteinuric diabetic patient with FSGS (case 1).

Case 1: Nephrotic Syndrome due to FSGS in Type 2 DM Patient

A 46-year-old male detected to have Type 2 DM three years ago presented with swelling of the legs of nine months duration. He denied family history of diabetes, hematuria, peripheral neuropathy or systemic illness. Physical examination revealed BP 170/100 mm Hg, edema ++, pallor +, and preproliferative diabetic RP. Systemic examination was unremarkable. Urinalysis showed 4+ proteinuria with 24 hrs urinary protein of 6.8 gm. Laboratory investigation revealed hemoglobin 12.8 gm/dL, total leukocyte count 10,200/m^3, serum creatinine 1.2 mg/dL, serum protein 5.6 gm/dL, serum albumin 2.9 g/dL, fasting blood glucose 186 mg/dL, serum calcium 7.8 mg/dL and serum phosphorus 3.4 mg/dL. Viral markers like HBSAg, Anti-HCV, Anti-HIV and Anti-CMV antibodies were negative. Immunological assays like ANA, Anti-ds DNA, C3, C4, and ANCA were negative. The clinical diagnosis of nephrotic syndrome related to Type 2 DM was made. Precutaneous renal biopsy was done histopathology revealed no evidence of DGS. Glomeruli showed feature consistent with diagnosis of focal segmental glomerulosclerosis with chronic tubulointerstitial nephritis. He was treated with amlodipine (10 mg/day), prazosin (5 mg/day), glibenclamide (5 mg/day) along with frusemide (80 mg/day). Oral prednisolone was started in a dose of 2 mg/kg on alternate days for treatment of FSGS in November 2004. The 24-hr urinary protein gradually decreased to 1.2 gm/day from initial value of 6.8 gm/day over a period of four months. Prednisolone was tapered and discontinued after six months. The 24-hour urinary protein was 386 mg at the end of 7 months follow up. The nephrotic syndrome was in continued remission with proteinuria of 300 to 488 mg/24 hrs during the follow-up period of six years. At last follow up in January 2010, 24-hour urinary protein was 332 mg, Hb 13.8 g/dL and serum creatinine 1.2 mg/dL. He is still continuing with oral hypoglycemic drug and antihypertensive medication with good control of diabetes and blood pressure, respectively. The salient laboratory feature of this patient is shown in Table 3.

We have observed remission of massive proteinuria and complete reversal of acute renal failure (ARF) in a Type 2 diabetic patient with histological diagnosis of chronic interstitial nephritis with minimal change disease treated with steroid (case 2).

Case 2: Nephrotic Syndrome with Interstitial Nephritis in Type 2 DM Patient

A 45-year-old gentleman, known diabetic and hypertensive since February 2004, was admitted on 27th February 2009 with complaint of swelling of both legs for 5 months as well as decreased urine output, nausea and breathlessness for 10 days. He was on amlodipine 5 mg daily for five years and glipizide 5 mg daily for two months. His laboratory investigations revealed 8.9 g/day proteinuria with bland urinary sediment, normal hemoglobin and leukocyte count with blood urea and serum creatinine of 118 mg/dL and 4.1 mg/dL respectively, serum albumin of 1.8 g/dL and bilateral normal size kidneys. In the next two days, he became oliguric with increasing uremia and was put on hemodialysis. There was no evidence of diabetic RP, systemic infection and obvious cause of acute renal failure. Kidney biopsy was done and light microscopy revealed chronic tubulo-interstitial nephritis with minimal change disease. He was treated with IV pulse methyl prednisolone followed by oral deflazacort. His renal function gradually improved and he was off dialysis in April 2009 (Blood urea and serum creatinine of 140 mg/dL and 3.6 mg/dL, respectively). Proteinuria decreased to 0.8 gm/day in August 2009 and to 0.6 gm/day at last follow up on 25th January 2010. He developed pulmonary tuberculosis and was started on four drugs ATT (RHEZ) on 25th January 2010. His renal function is normal till this date with proteinuria ranging from 300 to 500 mg/24 hour. His salient laboratory investigations are shown in Table 4.

In addition, symptomatic treatment for fluid and salt retention (diuretic and salt restriction), safe antihypertensive drugs for control of blood pressure. When the diabetic patient has reached the stage of renal failure, he/she usually suffers from multiple medical problems caused by diabetic microvascular and macrovascular complications. These are summarized in Table 5. It is obvious that complications of diabetes are much more common in patients with diabetes when they have DN. Thus, in addition to specific measures directed at managing kidney failure, intensive effort must be directed at identification and management of these

Table 3. Lab parameters of case 1 during follow-up period

Parameters	*Oct. 2004*	*Jan. 2005*	*Mar. 2005*	*May 2005*	*Jun. 2005*	*Dec. 2005*	*Jan. 2010*
Hb (gm/dL)	12.6	12.8	13.0	13.0	13.7	13.2	13.8
Urinary protein (g/24 hrs)	6.8	3.4	1.2	1.0	0.386	0.488	0.332
S. creatinine (mg/dL)	1.2	1.4	1.3	1.2	1.3	1.2	1.2
S. albumin (g/dL)	2.8	3.1	3.6	3.5	3.7	3.2	3.5
Blood pressure (mm Hg)	170/100	140/80	130/70	140/90	140/85	130/90	140/80
Oral prednisolone in dose of 2 mg/kg alternate day was started November 2004.							

Table 4. Lab parameters of case 2 during follow-up period

Date 2009-2010	*Bl. Glucose mg/dL*	*Bl. Urea mg/dL*	*S. Creat. mg/dL*	*S. Na^+ mmol/L*	*S. K^+ mmol/L*	*Hb% gm/dL*	*TLC/ cu.mm*	*Proteinuria g/ day*
Feb 19, 2009	129	76	**2.24**	125	3.1	13.7	6800	-
Feb 27, 2009	134	118	**4.1**	114	2.9	14	6500	**8.9**
Mar 6, 2009	114	132	**6.8**	123	4.5	-	-	-
Mar 15, 2009	104	90	**7.1**	132	2.2	-	-	-
April 3, 2009	116	140	**3.6**	136	4.2	13.4	-	**5.0**
April 22, 2009	128	107	**1.1**	132	2.9	14.1	-	**2.6**
May 16, 2009	118	28.9	**0.8**	136	4.5	13.0	-	**1.4**
Aug 11, 2009	105	21.8	**0.9**	-	-	12.5	-	**0.8**
Dec 7, 2009	127	28.7	**1.0**	128	5.3	9.9	-	**0.48**
Jan 25, 2010	106	32.1	**0.93**	123	6.4	11.2	-	**0.6**

problems as listed in Table 5. Regular examination of eyes and feet as well as assessment of vascular disease is vital. The control of blood pressure is difficult, requiring multiple drugs in patients with diabetic ESRD. Diabetic patients with renal failure carry the risk of hypoglycemia and use of metformin is associated with risk of lactic acidosis. Insulin, usually in low dose is being used to achieve satisfactory blood glucose control. Malnutrition and anemia should be treated appropriately. Renal osteodystrophy is relatively rare in diabetic: it takes a long time for the parathyroid glands to become overactive and kidney failure develops relatively quickly in diabetics. However, it may be necessary occasionally to treat kidney bone disease with calcium or vitamin D. Renal Replacement Therapy (RRT) should be started earlier in people with diabetes as compared to people without diabetes (when GFR is approximately 15 ml/minute). An even earlier start may be justified in individual case if fluid overload and blood pressure are very difficult to control. Severe anorexia and persistent vomiting due to kidney failure or delayed emptying of stomach (gastroparesis) is another indication for early dialysis. It is important to make an individual decision as to when to begin dialysis based on the patient as a whole and not to rely simply on level of kidney function.

The treatment options for diabetic ESRD are; (i) Hemodialysis, (ii) Continuous Ambulatory Peritoneal Dialysis (CAPD) and (iii) Renal transplantation. There is no doubt that kidney transplantation particularly combined with pancreas transplantation, provides optimal survival and the best quality of life. The combined kidney and pancreas transplantation is certainly the optimum procedure for young person with Type 1 DM. However, transplantation performed in older people with Type 2 diabetes is usually kidney transplant alone. Unfortunately, because of limited availability of organs, the great majority of people with Type 2 diabetes are not given transplant but treated by either hemodialysis or CAPD.

Table 5. Common-associated problems in Type 2 diabetic patients with diabetic nephropathy

Microvascular complications
Retinopathy (nonproliferative, proliferative)
Polyneuropathy including autonomic polyneuropathy
Cystopathy (detrusor paresis)
Gastroparesis
Neuropathic ulcer (diabetic foot)
Impotence
Macrovascular complications (Atherosclerosis)
Coronary heart diseases
Cerebrovascular disease
Peripheral vascular diseases
Ischemic nephropathy (renal artery stenosis and cholesterol microembolism)
Others
Hypertensive/nonhypertensive cardiomyopathy

KEY POINTS

1. In contrast to Type 1 DM, NDRD is common in patients with Type 2 DM and its prevalence varies widely from 27 to 79 percent.
2. Based on biopsy finding, three categories of renal diseases are described in patients with Type 2 DM: (1) isolated DN, (2) isolated NDRD and (3) NDRD superimposed on DN.
3. Clinical predictors of NDRD in Type 2 diabetic patients includes; (i) microhematuria, (ii) active urinary sediments, (iii) rapid loss of renal function, (iv) low serum complement level (v) nephrotic syndrome and/or massive proteinuria with normal renal function and (vi) impaired renal function with minimal or no proteinuria.
4. Presence of diabetic RP does not imply presence of DN in Type 2 DM. Because 40 to 50 percent of patients with DN do not have RP and nearly one third of patients with diabetic RP has isolated NDRD.
5. Renal biopsy is indicated in proteinuric Type 2 diabetic patients regardless of RP for precise diagnosis of DN *vs* NDRD in these patients.
6. Early biopsy diagnosis of NDRD is crucial because appropriate therapy is associated with good clinical outcome.
7. 40 percent to 60 percent of ESRD in Type 2 diabetic patients is associated with nondiabetic primary renal diseases. Since clinical courses of diabetic and nondiabetic ESRD are different; their precise diagnosis is essential from prognosis point of view.
8. Diabetic RP is a poor predictor of type of nephropathy in proteinuric Type 2 diabetic patients.
9. Remember, kidney involvement in Type 2 diabetic patients is not always caused by DN.

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SECTION 3

RENAL FAILURE

- Pathophysiology, Prevention and Treatment of Progressive Renal Failure Associated with Severe Congestive Heart Failure
- Acute Intrinsic Renal Failure
- A Reversible Syndrome of Acute Renal Failure Associated with Renin-Angiotensin Inhibitor Drugs
- Chronic Renal Failure: Clinical Perspective, Prevention, and Nondialysis Treatment
- Effect of Proteinuria on Renal Function in Diabetic and Nondiabetic Renal Disease
- Cystic Diseases of the Kidney
- Acute and Chronic Urinary Tract Obstruction in Adults: Pathophysiology, Diagnosis and Management
- Pathogenesis and Management of Bleeding Disorders in Renal Failure
- Renal Osteodystrophy
- An Overview of Leptospirosis: Renal and Hepatic Syndrome
- Drug Dosing in Renal Disease

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Pathophysiology, Prevention and Treatment of Progressive Renal Failure Associated with Severe Congestive Heart Failure

Anil K Mandal

ABSTRACT

This chapter describes an intricate association between severe congestive heart failure (CHF) and progressive renal failure. Renal failure is a consistent accompaniment of CHF. Renal failure progresses as CHF worsens. Although the exact mechanism of progressive renal failure in CHF is not well understood, angiotensin converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB) drugs, which are most commonly used in CHF to improve heart function, have severe adverse effects on renal function and electrolyte balance. These adverse effects are mainly caused by decreased blood pressure (BP) and decreased levels of angiotensin II and aldosterone. As a result of progressive renal failure, patients become volume overloaded, which gives rise to increased shortness of breath, warranting repeated hospitalizations. Hyponatremia is a common feature in CHF, which, along with hyperkalemia, caused by ACEI/ARB, predispose these patients to ventricular arrhythmias and sudden death. This study focuses on the importance of renal replacement therapy (RRT) as an alternative therapy to provide symptomatic relief by reducing fluid overload and to maintain electrolytes balance, thereby reducing the risk of ventricular arrhythmias.

PATHOPHYSIOLOGY OF RENAL FAILURE, FLUID OVERLOAD, AND ELECTROLYTE IMBALANCE IN SEVERE CHF

Renal failure is a consistent accompaniment of CHF. Renal failure progresses as CHF advances. Progressive renal failure is at least partly due to therapy of a combination of ACE inhibitors or ARBs and diuretics. Persistently low BP caused by the above drugs is a fundamental mechanism of decreased RBF and increased renal vascular resistance, which leads to sustained renal failure. Progressive renal failure associated with hypoalbuminemia, which is also common in CHF, is the pathophysiologic basis of inadequate response to diuretic therapy and decreased renal clearance of sodium and water, thereby giving rise to sustained or recurrent fluid overload. Consequently, frequent hospitalization is common in severe CHF patients seeking temporary relief for increased shortness of breath. Hyperkalemia, which is most commonly due to the use of ACE inhibitors or ARBs in the face of impaired renal function, remains a continuous threat for ventricular arrhythmias. Severe or life-threatening hyperkalemia is especially common with the use of a combination of an ACE inhibitors or ARB and spironolactone.

Severe CHF patients typically show slight elevation of serum creatinine level in the early stages but disproportionately more elevation of BUN. The greater elevation of BUN is the result of excessive reabsorption of urea facilitated by slow urine flow and increased level of antidiuretic hormone (ADH), which is common in severe CHF. Effective circulating blood volume (ECBV) is decreased as a result of excessive use of diuretics. Decreased ECBV and decreased cardiac output from poor heart function are responsible for low BP, which is a common finding in severe CHF patients. ACE inhibitors or ARBs reduce BP further by the suppression of angiotensin II and aldosterone. Renal blood flow (RBF) decreases in proportion to the decrease in BP.

Glomerular filtration rate (GFR) decreases in parallel with RBF.

In CHF, distal renal tubules exert a more dominant role than the proximal tubules in the retention of sodium and water prompted by the high level of aldosterone. High aldosterone levels also enhance urinary potassium loss, causing hypokalemia, which is common in severe CHF until renal failure is advanced. More importantly, use of ACE inhibitors or ARBs results in suppressed aldosterone level and consequently decreased urinary potassium excretion and hyperkalemia. ADH release is heightened by hypoxic stimulation of the hypothalamus as well as increased volume receptor signaling from decreased ECBV. Slow urine flow, decreased delivery of diuretics to the renal tubules, and increased ADH activity promoting excessive water and urea reabsorption in the collecting tubules, thereby further aggravating fluid overload, hyponatremia, and azotemia. Serum sodium is characteristically low in severe CHF. Persistent hyponatremia is a poor prognostic indicator in CHF.

Diuretic therapy constitutes an important part of medical management in severe CHF. However, response of diuretic therapy declines in parallel with the decrease in renal function, mainly due to decreased delivery of diuretics at the site of action in the tubules. Concomitant hypoalbuminemia due to malnutrition (inability to eat) and urinary protein loss attenuates the binding of diuretics to albumin, which is essential for the delivery of diuretics in the loop of Henle. Aldosterone antagonists such as spironolactone, promote the response of diuretics by inhibiting distal sodium and water reabsorption to some extent, but overall diuretic response still remains less than optimal. On the contrary, use of spironolactone in the presence of progressive renal failure carries a high risk of hyperkalemia, even life-threatening hyperkalemia and death. The publication of RALES (Randomized Aldactone Evaluation Study) was not associated with significant decreases in the rates of readmission for CHF or death in all cases. The risk of azotemia is highest in patients who are most dependent on the renin-angiotensin system for support of renal physiology. Derailment of renal physiology induced by CHF and further aggravated by angiotensin blocking drugs leads to a pathologic state of fluid and electrolyte balance, such as hyponatremia, hyperkalemia, metabolic acidosis, and anemia. A remarkable correlation has been reported between the severity of renal failure and cardiac mortality.

Pathophysiology and Adverse Effects of Anemia in CHF

Most patients with CHF are anemic, showing a hemoglobin level of less than 12 g/dL. Causes of anemia include dilutional from volume overload, slow gastrointestinal bleeding due to intake of aspirin and clopidogrel (Plavix®); use of ACEI/ARB, and, most importantly, progressive renal failure. ACEI/ARB and renal failure cause decreased erythropoietin (EPO) production. In addition, ACEI increases N-acetyl-seryl-aspartyl-lysyl proline, a natural peptide that decreases red cell precursors. Further, many patients with CHF also have uncontrolled diabetes mellitus. Patients with CHF who have diabetes are 2 to 4 times more likely to develop anemia than patients without diabetes. Increased blood glucose damages the EPO producing cells in the kidney, thereby decreasing the production of EPO. It is important to recognize and promptly treat anemia with exogenous EPO (Epogen®, Procrit®). The SOLVD study has shown that use of ACEI increased the risk of developing anemia by 56 percent, and this was associated with a significant increase in mortality rate. Other comorbidities associated with anemia include decrease in BP; increase in cardiac output, as well as heart rate and pulmonary capillary pressure with the risk of superimposed acute CHF. Anemia can also cause hyponatremia and peripheral hypoperfusion. All of these are risk factors for high mortality in CHF.

Impact of Renal Failure on the Conduction System of the Heart

Chronic kidney disease has a serious impact on the conduction system of the heart, including prolongation of PQ and QRS intervals and a higher prevalence of left bundle branch block. Another important feature is progressive diastolic dysfunction.

Importance of B-type Natriuretic Peptide (BNP) and N-terminal proBNP (NT-proBNP) in Determining Onset or Progression of CHF in Patients with Chronic and Progressive Renal Failure

BNP and NT-proBNP are established markers for CHF. In the setting of impaired renal function, the accuracy of BNP and NT-proBNP in predicting the onset or severity of CHF is reduced. Also, the prognostic accuracy for mortality with chronic renal failure is not yet determined.

In patients with CHF, values of both BNP and NT-proBNP were significantly higher in patients with moderately to severely impaired renal function ($P < 0.01$

for both comparisons). This study in a cohort of 831 dyspnea patients revealed, firstly, that the accuracies of NT-proBNP and BNP concentrations are similar for diagnosing CHF across a spectrum of renal function. Secondly, the clinician-selected patient population was similar for both BNP and NT-proBNP to diagnose CHF in patients with eGFR <60 ml/min. Thirdly, both tests can predict all cause one-year mortality. However, NT-proBNP better differentiates this risk in patients with impaired renal function than BNP.

Review of literature provides the information that BNP is elevated when CHF develops in a patient with advanced renal failure. But BNP assay is not found to be helpful in determining improvement in CHF during the course of therapy for renal failure, such as hemodialysis treatment. A patient is presented here to illustrate that scenario. A 53-year-old African-American female (AAF) was admitted to a local hospital on August 16, 2010, for increased shortness of breath. She is obese and has a long history of uncontrolled diabetes. Upon admission, her arterial blood gas was consistent with chronic respiratory acidosis mainly due to obesity. A random serum chemistry showed sodium 137 mmol/L, potassium 4.7 mmol/L, carbon dioxide 31 mmol/L, glucose 167 mg/dL, BUN 49 mg/dL, serum creatinine 4.29 mg/dL with eGFR of 11 ml/min, BNP 1650 pg/mL, and troponin was <0.04 ng/mL.

An echocardiogram on August 23, 2010, showed normal left ventricular size and function with ejection fraction of 60 percent. Because of clinical evidence of CHF associated with elevated BNP in the face of end stage renal disease, a tunneled dialysis catheter was placed and started on daily hemodialysis. First hemodialysis treatment was incomplete due to catheter malfunction. Here the serial BNP results:

53AAF Serial BNP (pg/mL) Results

August 2010	*Predialysis*	*4h-Postdialysis*
16th	1650	
	hemodialysis started	
20th	1350	1410
21st	1960	2470
22nd	1970	
23rd	1570	
25th	1300	
Discharged from the hospital; continues maintenance hemodialysis in the clinic. After several daily hemodialysis, BNP is slightly decreased.		

She was readmitted in the hospital on September 9, 2010, for vomiting and diarrhea. She denies shortness of breath. Blood gas analysis in room air on September 11 showed PO_2 77 mmHg, O_2 saturation 95.7 percent, but elevated PCO_2 of 63 mmHg. Her BNPa was 1020 pg/ml. It appears that BNP decreases with improvement in CHF by hemodialysis.

PREVENTION AND TREATMENT

Mild to moderate renal insufficiency (serum creatinine ≤ 2 mg/dL, eGFR between 30 and 50 ml/min) is a concomitant feature of CHF. Renal insufficiency may progress to end-stage renal disease (eGFR < 15 ml/min) with excessive use of ACEI, ARB, or a combination of both as sometimes prescribed by cardiologists trying to improve heart function. As a result, diuresis is impaired, and BUN and serum creatinine levels continue to increase. Then the nephrologists are consulted who prescribe a combination of diuretics, such as furosemide, bumetanide, or torsemide with metolazone, trying to promote diuresis. Diuretic therapies, including intermittent intravenous boluses, produce less than optimal results in the presence of ACEI/ARB therapies. The decreased BP due to low angiotensin II level caused by ACEI/ARB therapies gives rise to decreased RBF. Low dose ACEI/ARB alone is less harmful than combination of ACEI/ARB on renal function. Therefore, preventive measures include avoidance of the use of ACEI/ARB or a combination but use a combination of loop diuretics and distal tubule diuretics, such as metolazone, to promote diuresis. Loss of free water will increase serum sodium level. Hypokalemia is a common finding in CHF treated with excessive diuretic therapy. Therefore, addition of aldosterone antagonist, such as spironolactone 12.5 mg to 25 mg po. bid or amiloride 1.25 to 2.5 mg po; bid will minimize hypokalemia and potentiate the overall diuretic response. Risk of hyperkalemia, metabolic acidosis, and anemia is much less common when they are used without ACE/ARB than with them. Adequate control of blood glucose with insulin is essential to prevent further deterioration of renal function and worsening of anemia. Similarly, ACEI/ARB therapy shall be avoided to protect remaining renal reserve. When chronic renal failure is advanced to end stage renal disease, the preventive measures already stated are unlikely to produce any response to patient's comfort. At this stage, the following therapeutic strategies are considered:

1. Diuretic infusion
2. Continuous veno-venous hemofiltration (CVVH)
3. Intermittent hemodialysis (HD)
4. Continuous ambulatory peritoneal dialysis (CAPD)

Diuretic (furosemide or bumetanide) infusion is likely to produce adequate response, if the initial eGFR is more than 30 ml/min. Adequate response is defined by urine output of 3 to 4 liters per day. Diuretic infusion is prepared in normal saline or 5 percent dextrose in water, if not diabetic, in 500 ml bag with 240 mg furosemide or 12 mg bumetanide in the bag and infused at a rate of 21 ml (delivering 10 mg of furosemide or 1 mg of bumetanide) per hour. The response starts within 24 h and reaches its peak in 72 hrs. Potassium chloride 20 mEq in case of normal saline or 40 mEq in case of 5 percent dextrose in water is added to the bag to prevent hypokalemia. In those who are diabetic and 5 percent dextrose solution is used as a vehicle, 20 units of regular insulin is added to the bag to prevent severe hyperglycemia and its impact on renal function. As diuretic response reaches its peak, replacement fluid in the form of 0.9 percent or 0.45 percent saline solution is infused at a rate of 50 to 60/h to reduce the risk of volume depletion.

An essential component of the management plan of CHF is treatment of anemia with 20,000 units of Epogen® or Procrit® subcutaneously every 48 h or three times a week depending on the severity of anemia and until hemoglobin reaches 12 g/dL. It has been noted that, with epoetin alfa therapy, hemoglobin significantly increases and is accompanied by significant increase in ejection fraction of the heart, decrease in NYHA class of CHF, reduced days in hospital, and essentially no change in renal function.

Objectives of Renal Replacement Therapy (RRT) in Severe CHF (Figure 1)

1. RRT treatment is an established modality capable of adequately maintaining fluid and electrolyte balance in end-stage renal disease. Thus, it is most likely to alleviate the symptoms of fluid overload, namely

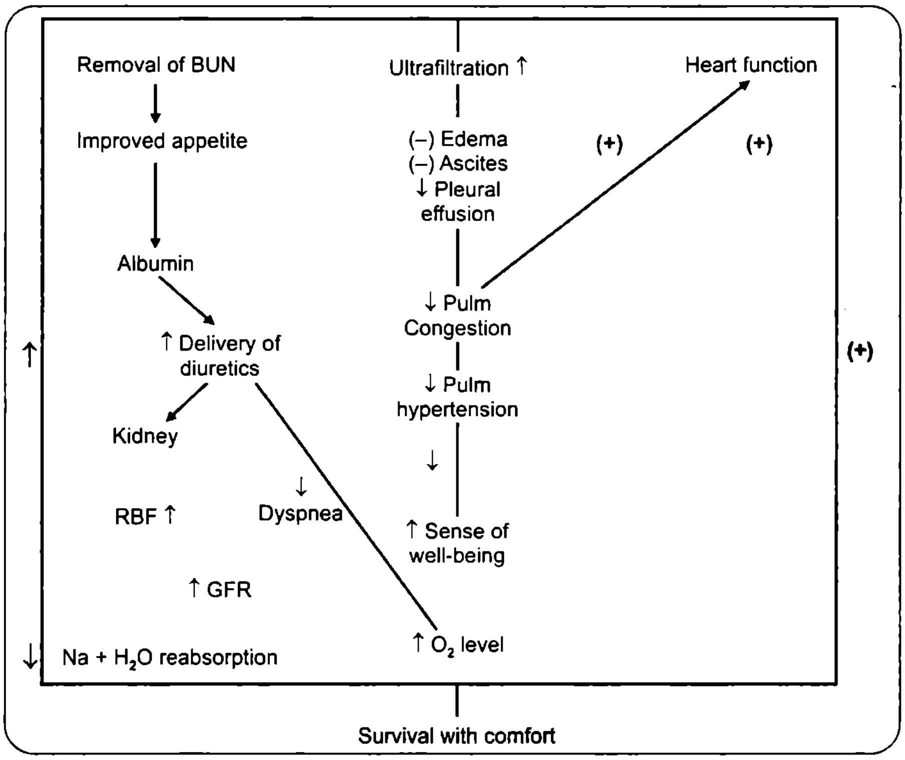

Figure 1: Mechanism of expected benefit of dialysis therapy. The benefit of dialysis therapy is attributed to removal of BUN, acid-base, and fluid controls. Removal of BUN results in improved appetite and increased serum albumin, which increases diuretic effect and improves survival. Acid-base control reduces the risk of ventricular arrhythmias, and fluid control reduces pulmonary congestion and shortness of breath

dyspnea, thereby reducing frequent hospitalization and possibly reducing death from hypoxia and arrhythmias.

2. Dialysis treatment by reducing the nitrogenous waste products, which are toxic to heart, gastrointestinal tract, brain, and hematopoietic system, is likely to improve the pump function of the heart, improve appetite, increase sense of well being, and permit correction of anemia.
3. When the above benefits are accomplished, inotropic drugs, such as Digoxin® and diuretics, are likely to be more effective in the maintenance of the benefits already accomplished. However, this hypothesis needs to be tested. Overall, ACEI/ARB drug therapy should be avoided to maintain good urine flow and reduce the risk of hyperkalemia, including life-threatening hyperkalemia.

Brief Review of Dialysis Therapy in CHF

A variety of dialysis modalities, including hemodialysis, CVVH, intermittent peritoneal dialysis (IPD), and CAPD, were tried in the past to treat fluid overload for symptomatic relief in severe CHF. Among all the dialysis modalities, CAPD was tried most often. Treatment was limited to a small number of patients, and most were short-time studies. Nonetheless, cumulative results of these studies are convincing and should stimulate further long-term trials of RRT in end stage renal disease associated with severe CHF.

The benefits of CAPD include improvement in renal function, increased diuretic response, a significant decrease in hospitalization rate, an increase in ejection fraction, and a decrease in NYHA class of CHF from IV to II. Also, there is a general consensus among these reports on the improvement in symptoms and general well being of the patients. For instance, hospitalization decreased from 78.7 ± 16.8 to 28.7 ± 17.1 days per year. Mean survival time on CAPD was 17.3 ± 4.1 months for patients who die. Mean dialysis time for patients who remained on dialysis was 16.2 ± 0.7 months. In another study involving 16 patients with class III or IV NYHA CHF, peritoneal dialysis significantly prolonged survival.

Symptomatic improvement also can be obtained with HD or CVVH. However, rapid flow system underlying HD or CVVH is likely to give rise to arrhythmias in patients with severe CHF. Therefore, CAPD or IPD is distinctly safer than hemodialysis or CVVH. However, CAPD requires a support system, which is always not available, and IPD requires hospital admissions. CVVH is a cumbersome procedure and can be done only in an intensive care setting. Thus, CVVH is not a popular method among the nephrologists. Therefore, maintenance HD is considered as the most optimal therapy for treatment of end-stage renal disease associated with CHF. However, no reports of controlled or long-term studies are available to validate the effectiveness and safety of this therapeutic modality in end-stage renal disease associated with severe CHF. Intermittent HD is done as an outpatient, requires no training for the patients and their families and, with availability of transportation, this therapy is most commonly accepted by the patient and their families as well as by the nephrologists. The common disadvantages are frequent hospitalization for access revision and infections, which increase the cost of care. If HD is initiated in very advanced stage of CHF with ejection fraction of less than 20 percent, risk of ventricular arrhythmias and sudden death during or immediate postdialysis is high.

Two patients are briefly presented here to illustrate benefits of RRT in progressive renal failure associated with severe CHF.

PATIENTS' PRESENTATION

Patient #1

A 46-year-old white male with a history of ischemic cardiomyopathy, class IV CHF and diabetes mellitus, had a total of eleven admissions for severe CHF into the intensive care unit of a local hospital in Jacksonville, Florida, extending from February 21, 2000, to April 24, 2001 (total period = 14 months). All admissions were warranted by increased shortness of breath, massive edema, and deteriorating renal function. A nephrology consultation was obtained at admission number 4 for worsening renal function. Therapy in admission number 1 included spironolactone 12.5 mg po twice daily, captopril 25 mg po three times daily, digoxin 0.125 mg po once daily, clopidogrel (Plavix®) 75 mg po once daily, omeprazole (Prilosec®) 20 mg twice daily, regular insulin as per sliding scale, and dobutamine infusion. Serum chemistry showed creatinine 1.4 mg/dL, sodium 133 mmol/L, potassium 4.8 mmol/L, fasting glucose 310 mg/dL. In subsequent admissions, metolazone 5 mg po three times daily, bumetanide 2 mg po three times daily were added, spironolactone increased to 12.5 mg po three times daily, enalapril 2.5 mg po three times daily, carvedilol 12.5 mg po twice daily, and simvastatin 10 mg po daily also were added. Serum chemistry showed BUN 79 mg/dL, creatinine 1.4 mg/dL. Furosemide 80 mg IV q 12h and milrinone infusion were initiated. On admission number 4, abdominal paracentesis was done with removal of large volume of ascitic fluid for symptomatic relief. Paracentesis was followed by a marked decrease in BP, systolic BP ranged between 70 and 80 mm Hg. Serum chemistry showed BUN 128 mg/dL, creatinine 5.3 mg/dL, sodium 129 mmol/L, potassium 4.7 mmol/L, chloride 89 mmol/L, CO_2 20 mmol/L, anion gap of 20 mmol/L (metabolic acidosis), hemoglobin 9.1 g/dL, hematocrit 21.7 percent, total protein 6.7 g/dL, albumin 3.8 g/dL. Furosemide and metolazone were put on hold for hypotension. CVVH, hemodialysis, or CAPD was recommended. The patient refused any form of interventional therapy and was admitted to hospice care. Soon he elected to end hospice care and agreed to hemodialysis treatment. He was severely dyspneic, grossly volume overloaded with weeping ulcerations on the lower extremities. A serum chemistry showed BUN 218 mg/dL, creatinine 6.6 mg/dL, potassium 6.4 mmol/L, and bicarbonate 17 mmol/L. Hemodialysis treatment was started. The patient tolerated hemodialysis well and showed decrease in edema and ascites. His medical management was titrated downward. However, hemodialysis became technically difficult because of persistent hypotension. Dopamine and albumin infusions failed to increase BP sufficiently to carry on hemodialysis. He developed Klebsiella bacteremia and severe hypotension and expired soon thereafter.

Patient #2

An 80-year-old white female was brought to the emergency room of a local hospital in Palatka, Florida, on January 17, 2002, for increased shortness of breath and was admitted to the intensive care unit. She had history of hypertension, CHF, and atrial fibrillation. Her significant past history consisted of myocardial infarction x 2. Therapy prior to admission included furosemide 40 mg po bid, ramipril (Altace®) 10 mg po daily, metolazone 5 mg po daily, digoxin 0.125 mg po daily, metochlorpropamide 10 mg po daily at bedtime, and micro-K 10 mEq po daily. Serum chemistry upon admission showed BUN 96 mg/dL, creatinine 5.3 mg/dL, glucose 101 mg/dL, calcium 9.4 mg/dL, sodium 129 mmol/L, potassium 8.0 mmol/L, chloride 92 mmol/L, and CO_2 22 mmol/L. A repeat serum potassium at 10:39 p.m. was 8.2 mmol/L. An electrocardiogram showed atrial fibrillation. Initial treatment consisted of intravenous administration of calcium gluconate 10 percent 20 ml and infusion of 5 percent dextrose in half-normal saline with one ampoule of sodium bicarbonate at 40 ml/h. Ramipril and micro-K were discontinued. Hemodialysis was initiated. Hemodialysis with no potassium in dialysis bath for 3 hours was carried out on January 18, 2002. A Chest X-ray prior to hemodialysis showed cardiomegaly, pulmonary congestion, and bilateral pleural effusion consistent with severe CHF. Following hemodialysis, she felt greatly relieved. Hemodialysis was continued on Mondays and Fridays for maintenance of fluid and electrolyte control and symptomatic relief. Discharge medications included amlodipine 5 mg po daily, spironolactone 25 mg po bid, micro-K 10 mEq po bid. Her 24-hour creatinine clearance progressively increased. She remained asymptomatic. Hemodialysis was discontinued on March 18, 2002, but was resumed on June 3, 2002, because of increased shortness of breath and an eight kilogram weight gain. She then continued her maintenance hemodialysis treatment regularly three times a week. In January 2003, one year after her first hemodialysis, she was completely asymptomatic, lived a comfortable life, and frequently traveled long distances with her daughter. Her 24-hour creatinine clearance as of January 30, 2003, was 25 ml/min. She maintained a urine volume of about 2 liters per day with diuretics. Strangely enough, her daughter experienced increased difficulties in transporting her to dialysis clinic, and her financial situation did not permit her to be a nursing home candidate. Her daughter decided to terminate her dialysis treatment. She died shortly thereafter.

This patient exemplifies that dialysis treatment can provide a comfortable survival, improve renal function, and increase diuretic response in patients with severe CHF. Her serial serum potassium levels are presented in Table 1. Table 1 illustrates that the patient was essentially hypokalemic. Hypokalemia is most likely due to hyperaldosteronism in severe CHF. Ramipril initially caused severe hyperkalemia by suppression of production of angiotensin II and aldosterone. Micro-K on top of ramipril further aggravated the hyperkalemia.

Table 1. Serial serum potassium levels in a 80-year-old white female

2002-2003	*Serum Potassium (mmol/L)*
January 17	8/8.2
Ramipril discontinued, Hemodialysis done.	
January 18	4.8
Hemodialysis: Mondays and Fridays	
January 20	3.8
January 23	2.8
Spironolactone 12.5 mg daily	
January 25	2.9
January 28	3.2
January 29	2.7
Spironolactone 25 mg po Q 6 h x 48 h, then 25 mg po tid	
January 30	3.8
February 2	4.0
February 3	4.4
Spironolactone decreased to 25 mg po bid	
February 4	4.3
June 4	3.6
Spironolactone increased to 25 mg po tid	
January 30	3.8

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17

Acute Intrinsic Renal Failure

Jai Prakash

INTRODUCTION

Acute renal failure (ARF) is defined as a rapid (i.e., over hours to weeks) and usually reversible decline in glomerular filtration rate (GFR) that can occur either in the setting of previously normal renal function ("classic" ARF) or in a patient with pre-existing chronic renal disease ("Acute-on-chronic" renal failure). Numerous definition of ARF has been published. The international Acute Dialysis Quality Initiative (ADQI) groups have provided useful definition for ARF and acute-on-chronic renal failure. This classification system uses GFR and urine output criteria, whichever is worse, to define three increasingly severe levels of renal dysfunction (Table 1). Patients are classified according to their risk of renal dysfunction, type of kidney injury, and degree of kidney failure, and two associated clinical outcomes: Loss and ESRD (RIFLE). Persistent ARF (Loss) is defined as the need for more than four weeks of renal replacement therapy (RRT); ESRD is defined as dialysis dependence exceeding three months.

CATEGORIES OF ACUTE RENAL FAILURE

ARF can result from decreased renal perfusion without cellular injury (pre-renal); an ischemic or toxic insult to the renal tubules (acute tubular necrosis); obstruction of the urinary outflow tract (postrenal); or due to primary intra-renal cause (intrinsic renal failure). Intrinsic renal diseases that result in ARF are categorized according to the primary site of injury; tubules, interstitium, vessels or glomerulus (Fig. 1). Pre-renal failure and acute tubular necrosis (ATN) due to ischemia and nephrotoxins are responsible for most episodes of ARF. Pre-renal azotemia accounts for approximately 70 percent of community-acquired cases of ARF and 40 percent of hospital-acquired cases. Hospital-acquired ARF is often

Table 1. RIFLE classification of ARF (ADQI 2004)

Categories	*GFR criteria*	*Urine output criteria*
Risk	S. creatinine x 1.5 or GFR decreases > 25%	<0.5 ml/kg/h for 6 hours
Injury	S. creatinine x 2.0 or GFR decreases > 50%	<0.5 ml/kg/h for 12 hours
Failure	S. creatinine x 3.0 or GFR decreases > 75% or S. creatinine > 4 mg% when acute increase > 0.5 mg%	<0.3 ml/kg/h for 24 hours or anuria for 12 h
Loss	Persistent ARF; complete loss of kidney function > 4 weeks	-
End-Stage Renal Diseases (ESRD)	ESRD > 3 months	-
RIFLE system classifies ARF into three severity categories (risk, injury and failure) and two clinical outcome categories (loss and ESRD).		

due to more than one insult. A wide spectrum of clinical conditions can result in reduced renal perfusion and subsequently ischemic ATN (Fig. 2). Sustained pre-renal azotemia is the most common factor that pre-disposes patients to ischemia-induced ATN. It is important to note that patients presenting with acute renal dysfunction without a baseline measure of renal function should be evaluated for the presence of chronic renal disease. This article will not discuss the pre-renal, postrenal and ATN. I shall provide an overview of intrinsic ARF involving the glomeruli, tubulointerstitial tissue and intrarenal vessels.

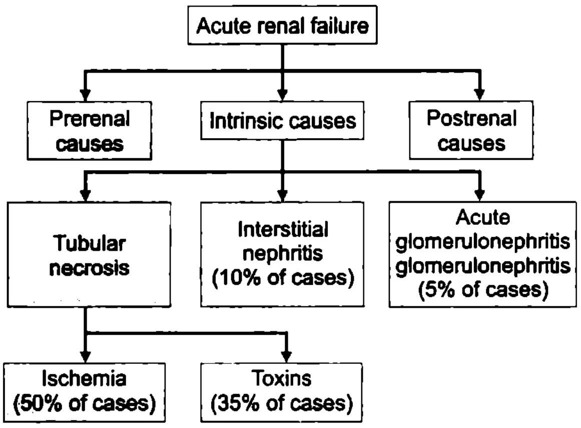

Figure 1: Main categories of acute renal failure (ARF)

Intrinsic Acute Renal Failure

Once pre-renal and postrenal causes have been excluded, one is left with intrinsic causes. The primary site of injury determines the nature of intrinsic ARF; interstitium (acute interstitial nephritis), vessels (renal vasculitis), glomerulus (acute glomerulonephritis) and renal cortex (renal cortical necrosis). However, the major cause of intrinsic ARF is ATN. The following conditions will be discussed in this review:

1. Acute Interstitial Nephritis (AIN)
2. Acute Glomerulonephritis (AGN)
3. Renal Vasculitis (RV)
4. Renal Cortical Necrosis (RCN)
5. ARF in certain specific situations
    a. Myeloma-associated ARF
    b. Pregnancy-associated ARF
    c. Liver disease-associated ARF

Acute Interstitial Nephritis

It is a common cause of acute kidney injury and histologically characterized by interstitial inflammation, edema and tubulitis. Many etiologies of AIN have been recognized, including allergic/drug-induced, infections, autoimmune/ systemic diseases and idiopathic form of the disease. The clinical features are often nonspecific and the "classical" triad of fever, rash and eosinophilia are now uncommon. AIN should be considered in case of

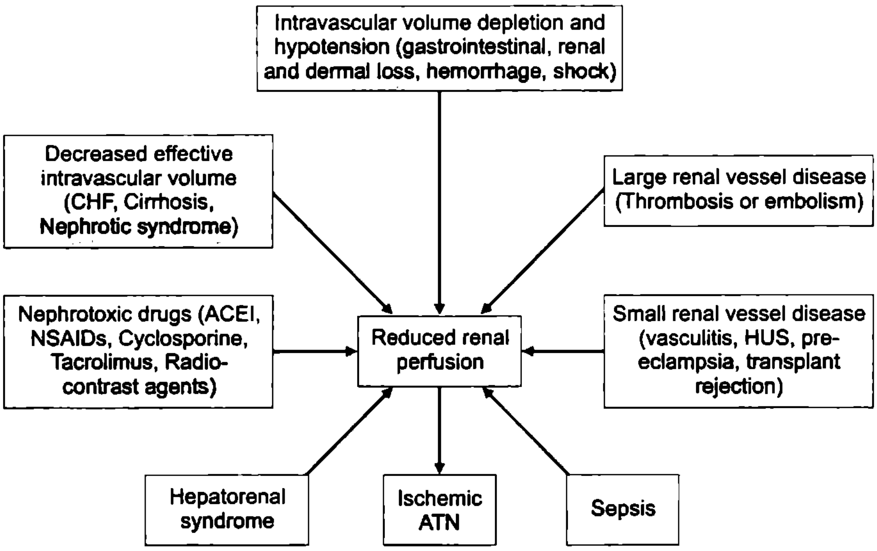
Intravascular volume depletion and hypotension (gastrointestinal, renal and dermal loss, hemorrhage, shock)
Decreased effective intravascular volume (CHF, Cirrhosis, Nephrotic syndrome)
Large renal vessel disease (Thrombosis or embolism)
Nephrotoxic drugs (ACEI, NSAIDs, Cyclosporine, Tacrolimus, Radio-contrast agents)
Reduced renal perfusion
Small renal vessel disease (vasculitis, HUS, pre-eclampsia, transplant rejection)
Hepatorenal syndrome
Ischemic ATN
Sepsis

Figure 2: Clinical condition that can lead to ischemic acute tubular necrosis (ATN). Diverse clinical conditions lead to ischemic ARF. Severe and sustained pre-renal azotemia is the most common condition leading to ischemic ATN

ARF, especially when there is no obvious precipitant. The renal outcome is usually good but in a small proportion of patients, particularly the elderly, significant renal impairment can persist. Etiology of AIN can be grouped in following four categories:

1. Allergic/drug induced
2. Infection associated
3. Autoimmune/systemic disease
4. Idiopathic

There are ever-increasing numbers of association with AIN requiring constant vigilance. Historically, prior to the widespread use of antibiotics, exposure to infective agents was the most frequent causes of AIN, but now drugs predominate. Based on a number of contemporary series, causes include:

- Drugs (71 percent)
- Infection (15 percent)
- Idiopathic (8 percent)
- Tubulointerstitial Nephritis and Uveitis (TINU) syndrome (5 percent)
- Sarcoidosis (1 percent)

Drug-induced AIN

The most common etiology of AIN is drug-induced disease, which is thought to underlie 60 to 70 percent of cases. Granulomatous interstitial nephritis (GIN) represents a histologically distinct variant of AIN with renal biopsy incidence of 0.5 percent. Similar to AIN, GIN most commonly has a drug-induced etiology. Drugs and sarcoid were responsible for GIN in a series of 46 patients at a single institution; and in that study, drug-induced GIN was caused mainly by treatment with antibiotics or nonsteroidal anti-inflammatory drugs (NSAIDs). The list of drugs commonly causing AIN is given in Table 2. Recent additions to the list include celecoxib, etanercept, sorafenib, linezolid and several anti-retroviral agents.

Clinical Features of Drug-induced AIN

The clinical feature of AIN varies with the class of drug involved. The only consistent clinical manifestation is acute or subacute kidney injury, often resulting in chronic kidney disease. The classical triad of AIN symptoms; fever, rash and eosinophilia; is typically seen in less than 5 to 10 percent of patients and depends on the class of drug causing AIN. For example, typical hypersensitivity syndrome (fever, rash and eosinophilia) is common with antibiotics (methicillin) but is rare in AIN caused by proton pump inhibitor (omeprazole) and fluoroquinolone (ciprofloxacin); and the triad is typically absent in those related to NSAIDs. Therefore, the absence of "classic" findings of AIN; fever, rash and eosinophilia; does not exclude drug-induced AIN in appropriate clinical setting. Overall, eosinophilia is present in 23 to 60 percent of individual, rash in 15 to 21 percent and fever in 27 to 30 percent. It is thought that the incidence of "classic" symptoms is less due to the reduced use of these antibiotics causing AIN.

There are numerous agents associated with drug-induced AIN (Table 2). Eighty percent of cases develop AIN within 3 weeks of starting the precipitant drugs, but the time of developing AIN following exposure ranges from 1 day to over 12 months. The development of drug-induced AIN is not dose dependent and can reoccur on rechallenging with the same or related drug, usually rapidly within two to three days. In NSAIDs associated AIN, the duration of therapy prior to the development of AIN is long, typically 6 to 18 (median 3) months. Extrarenal signs (fever and rash) and hematuria are rare with NSAID-induced AIN. However, it has been described even after application of topical NSAID preparation.

Urinalysis usually reveals proteinuria, although normally less than 2 gm/24 hr is excreted. Nephrotic range proteinuria (>3 gm/24 hr) can occur but should arouse suspicion of concomitant minimal change disease secondary to NSAID usage. Mild hematuria on urinalysis is common but macroscopic hematuria and red cell cast on microscopy are rarely found. White cells and white cell casts may also be present in the urine and examination for eosinophiluria (eosinophil >1 percent of total urine white cells) with Hansel's stain is often positive. Enlarged

Table 2. Common drugs causing AIN

Antibiotics	Penicillins, Cephalosporines, Rifampicin, Sulfonamides, Quinolones, Tetracycline
NSAIDs	Diclofenac, Ibuprofen, Neproxen, Indomethacin, COX-2 inhibitors
Diuretics	Loop and Thiazide
Anticonvulsants	Phenytoin, Carbamazepine, Phenobarbital
Antiviral drugs	Abacavir, Indinavir, Aciclovir, Atazanavir
Others	Proton pump inhibitors, H2 receptor antagonist, 5-aminosalicylates, Allopurinol, Captopril, Interferon, Cyclosporine

kidney is a nonspecific finding in AIN and may cause flank pain due to associated distension of the renal capsule.

Infection-related AIN (IR-AIN)

The advent of antibiotics is believed to have reduced the frequency of AIN cases caused by infection. A number of pathogens are associated with IR-AIN (Table 3). The infecting agents are thought to cause AIN by stimulating the release of chemokines leading to leukocyte infiltration of the interstitium. Histologically, it is identical to drug-induced AIN and the clinical presentation will depend upon the underlying infection.

Autoimmune AIN

Most autoimmune conditions associated with an interstitial infiltrate cause a chronic interstitial nephritis. However, several of these may also be associated with a more acute presentation (Table 4). Sacroidosis is a cause of granulomatous AIN. It is associated with extra-renal symptoms in approximately 90 percent of cases. Hilar lymphadenopathy and pulmonary infiltrate are found in around half of the patients.

Idiopathic AIN

Idiopathic AIN is a heterogeneous entity where a cause of interstitial nephritis is not clear. TINU syndrome was first reported in 1975 as an association between AIN and anterior uveitis, sometimes associated with bone marrow granuloma. It is a rare disease. Although associations with *Chlamydia*, *Mycoplasma* and Epstein Barr Virus infections have been suggested, the etiology remains obscure. The development of TINU syndrome have been described with exposure to some drugs (e.g., cephalosporine and NSAIDs) as well. It can be associated with some autoimmune conditions (e.g., hypothyroidism and thyroiditis). Uveitis is often bilateral and ocular symptoms may precede (21 percent), be concurrent with (15 percent), or occur after (25 percent) the AIN. Renal biopsy findings include granulomatous (13 percent), interstitial eosinophils (33 percent) and neutrophils (25 percent). The patients may suffer from weight loss and anemia and have a high ESR along with renal impairment, but presentation is often nonspecific.

ARF Due to Acute Glomerulonephritis/Vasculitis

Inflammatory disease of the glomeruli [glomerulonephritis (GN)] and renal microvasculature (Vasculitis) are important causes of intrinsic ARF, accounting for approximately 10 percent of cases. ARF associated with GN is common in small vessel vasculitis and Systemic Lupus Erythematosus (SLE); but is uncommon in other multisystem diseases. It is rare in association with primary glomerular diseases. From a clinical point of view, ARF in patients with GN/vasculitis is divided into four categories:

1. ARF due to GN
2. ARF due to vasculitis
3. ARF in patients with preexisting GN
4. ARF complicating nephrotic syndrome

1. **Causes of ARF due to Glomerulonephritis:** The causes of ARF associated with GN and crescents are listed in Table 5. The histological findings in ARF associated with GN include endocapillary proliferative lesions, crescentic GN, and focal necrotizing GN. In Europe and North America, small vessel vasculitis, SLE and Anti-GBM Ab associated diseases are the usual cause of ARF due to GN/vasculitis. However, infection associated GN is probably the most common cause worldwide. Acute poststreptococcal GN is the most common form of postinfectious GN, accounting for 10 to 20 percent of the ARF due to glomerular disease. It is

Table 3. Causes of infection-related AIN

Bacterial	*Streptococci*, *Staphylococci*, *Escherichia coli*, *Salmonella*, *M. tuberculosis* and *Leptospirosis*
Viral	Epstein Barr Virus, Cytomegalovirus, BK Virus, Hepatitis B Virus, Herpes Simplex Virus, HIV, Hantavirus and Measles
Others	*Mycoplasma*, *Toxoplasma*, *Leishmania donovani*, *Chlamydia*

Table 4. Causes of autoimmune related AIN

Systemic lupus erythematosus
Sjogren's syndrome
Sarcoidosis
Wegener's granulomatosis
Necrotizing vasculitis
Primary billiary cirrhosis
Acute graft (renal transplant) rejection
Essential cryoglobulinemia

more frequent in children than in adults. Idiopathic crescentic GN (extracapillary cell proliferation within Bowman's space) clinically present as rapidly progressive glomerulonephritis (RPGN) and can be classified into three groups on the basis of the underlying immunopathology: (i) Type 1, Anti-GBM Ab mediated; (ii) Type 2, Immune complex mediated; and (iii) Type 3 is characterized by absence of immune deposits (Pauci-immune). All patients who present clinically with RPGN or evidence of vasculitis should be submitted to renal biopsy and appropriate serological investigation as a matter of urgency. Assay for Anti-GBM Ab, Anti-Neutrophilic Cytoplasmic Antibody (ANCA), lupus serology and complements are particularly important. Making an accurate diagnosis of the cause of RPGN is critically important, as both the nature of the therapy and the response to treatment will be very different, depending on the precise diagnosis.

2. **ARF due to Vasculitis:** Vasculitis is a heterogeneous group of disorders characterized by inflammation, necrosis, and cellular infiltration of blood vessel. This process can affect large, medium or small vessels leading to destruction of the integrity of the vessel wall. The kidney is chiefly involved when small vessels (arterioles, capillaries, and venules) are affected. Renal vasculitis (RV) may be limited to kidney (renal limited vasculitis) or be part of a systemic disease. ANCA, either directed to myeloperoxidase (P-ANCA) or proteinase 3 (C-ANCA) can be detected in 80 to 90 percent of cases of RV. About 5 to 10 percent of otherwise typical cases of RV do not have detectable ANCA (ANCA-negative) and 5 percent of specimen may have anti-GBM Ab along with ANCA (double positive type IV RV). Systemic vasculitis accounts for only a small minority of cases of ARF (about 5 percent), but they can be associated with severe morbidity. The working classification of the glomerular and vasculitis syndrome associated with ARF is based on their pathogenetic mechanisms (Table 6). ANCA-associated (Pauci-immune) vasculitis includes: Microscopic Polyangitis (MPA), Wegener's Granulomatosis (WG), Churg-Strauss Syndrome (CSS) and Renal Limited Vasculitis (RVL). Most often, the clinical presentation is that of RPGN with or without signs and symptoms of extrarenal manifestation. The presentation of MP and WG is usually extrarenal; is always extrarenal in CSS; and is always renal in RVL. ARF is the most common form of renal presentation of ANCA-associated vasculitis.

Table 5. Acute renal failure (ARF) due to glomerulonephritis (GN)

1. **Immune-complex (IC) mediated diseases**
    - Postinfectious glomerulonephritis
    - Systemic lupus erythematosus
    - Cryoglobulinemia
    - Henoch-Schonlein purpura
2. **Anti-GBM antibody associated**
    - Goodpasture's syndrome
    - Anti-GBM disease
3. **Pauci-Immune glomerulonephritis**
    - Microscopic polyangitis (MPA)
    - Wegener's granulomatosis
    - Churg-Strauss syndrome
    - Renal limited vasculitis
4. **Miscellaneous**
    - Primary systemic vasculitis
    - Mesangial IgA nephropathy
    - Mesangiocapillary glomerulonephritis
    - Focal segmental sclerosis
    - Membranous nephropathy
    - Neoplasia associated – GN
    (Carcinoma, Lymphoma, Leukemia)

*Post infectious glomerulonephritis includes spectrum of proliferative glomerulonephritis associated with poststreptococcal disease, infective entocarditis, shunt nephritis and visceral abscess.

3. **ARF in patients with Underlying Glomerulonephritis:** The development of acute or acute-on-chronic renal failure in a patient known to have an underlying GN

Table 6. Causes of ARF due to vasculitis

1. Immune complex mediated vasculitis
    - Systemic lupus erythematosus
    - Cryoglobulinemic vasculitis
    - Henoch-Schonlein purpura
2. Anti-GBM antibody mediated-vasculitis
    - Goodpasture syndrome
    - Anti-GBM disease
3. Pauci-Immune small vessel vasculitis
    - Microscopic polyangitis (MPA)
    - Wegener's granulomatosis
    - Churg-Strauss syndrome
    - Renal limited vasculitis

needs careful assessment as the differential diagnosis is wide.

a. **Crescentic GN:** Superimposed crescent formation in patients with primary membranous nephropathy, mesangiocapillary GN and IgA nephropathy can cause rapid development of ARF.
b. **Hematuria:** Rapid deterioration of renal function especially during prolonged episodes of macroscopic hematuria has been reported in patients with IgA nephropathy.
c. **Acute interstitial nephritis:** AIN related to drugs (diuretics, NSAIDs, cimetidine, antibiotics) may cause ARF in patients with primary glomerular diseases.

Acute oliguric renal failure is infrequent, but may occur in patients with Henoch-Schonlein Purpura. Renal biopsy usually reveals a high proportion of crescents.

4. **ARF complicating Nephrotic Syndrome:** ARF complicates nephrotic syndrome more often than is generally appreciated. Renal failure may develop in the absence of glomerular inflammation and may occur either at the time of presentation or much later. The possible causes of ARF in nephrotic syndrome include; hypovolemia, ATN, drug induced interstitial nephritis, crescentic transformation of underlying glomerular disease and renal vein thrombosis. An important factor in hypercoagulable state is loss of antithrombin III in patients with nephrotic syndrome. Abnormal renal hemodynamics associated with nephrotic syndrome itself may cause ARF in most cases. The filtration fraction is reduced in nephrotic syndrome, which is attributed to increased intratubular or interstitial pressure secondary to interstitial edema. Sometimes renal failure reverses with aggressive treatment of edema with diuretics and recurs with accumulations of edema. Intratubular obstruction caused by intratubular protein casts is another hypothesis of ARF in nephrotic syndrome. Drugs used in managing nephrotic syndrome, including antibiotics, diuretics and cimetidine, can cause ARF by inducing interstitial nephritis. The hypercoagulable state, which accompanies nephrotic syndrome, predisposes to renal vein thrombosis.

Treatment of Glomerulonephritis/vasculitis-associated ARF

The treatment is divided into the following three groups; (i) General measures; (ii) Immunosuppressive therapy; and (iii) Plasmapheresis.

i. **General Measures:** It involves supportive and symptomatic treatment. Dialysis and ultrafiltration may be carried out for an acute uremic state or fluid overload. Antihypertensive drugs and diuretics are used for control of hypertension and edema. Antibiotics are indicated if there is evidence of infection. The use of H2 antagonists or proton pump inhibitors has become standard practice as prophylaxis against stress ulcer in patients with ARF and for those given high dose of steroids.
ii. **Immunosuppressive therapy:** Three major vasculitis syndromes have a common therapeutic protocol. Corticosteroid in combination with cyclophosphamide remains the mainstay of therapy for WHO class IV lupus nephritis, anti-GBM disease and ANCA-associated vasculitis. It is reasonable to minimize inflammation with prompt and aggressive therapy. Typically, patients are given IV pulse methylprednisolone (0.7 mg/kg/day x three days) followed by oral prednisolone. Prednisolone is started at a dose of 1 mg/kg/day for the first month, tapered to an alternate day regimen during the second month and discontinued by the end of three to four months. Cyclophosphamide is administered either orally (0.2 mg/kg/day) or monthly as an intravenous pulse at starting dose of 0.5 gm/m^2 body surface area for six months. After the first 6 months, pulse cyclophosphamide is given every 3 months for a total of 18 to 24 months. The dose is titrated upward during the first six months, increasing by 0.25 gm/m^2 on successive treatment (not exceeding 1.0 gm/m^2), provided that two-week leukocyte count remains about 3000 $cells/mm^3$. Once remission is attained, an alternative maintenance regimen consists of switching cyclophosphamide to oral azathioprine at the end of three months. Azathioprine is then continued for a total of 12 to 24 months. The combined immunosuppressive therapy with prednisolone and cyclophosphamide has improved the patient and renal survival to approximately 85 percent and 60 percent respectively, in patients with

anti-GBM disease. In Pauci-immune vasculitis, the rate of remission is 70 percent to 85 percent with the use of alkylating agents. Several recent trials have shown that mycophenolate mofetil (MMF) is useful in inducing remission of lupus nephritis and even the complete remission rate was higher in the MMF arm. In addition, MMF was also found to be superior during the maintenance phase of severe lupus nephritis, once remission was achieved. The dose of MMF is 2 to 3 gm/day in two divided doses in the induction phase and 0.5 to 1 gm twice daily during the maintenance phase of treatment. The major prognostic marker of progression to ESRD is serum creatinine level above 7 mg/dL at the time treatment is initiated. However, aggressive treatment should be continued for at least four weeks and discontinued in the absence of recovery of renal function by eight weeks, for those patients with an elevated serum creatinine (7 mg/dL) with cellular crescent on biopsy. The immunosuppression therapy should not be withheld, even with serum creatinine level above 7 mg/dL in patients with concomitant presence of anti-GBM antibody and ANCA because presence of ANCA may be associated with more favorable renal outcome.

iii. **Plasmapheresis:** The definite indication of plasmapheresis is pulmonary hemorrhage in patients with anti-GBM disease and pauci-immune vasculitis. It is typically performed daily until the pulmonary hemorrhage ceases and then every other day for a total of 7 to 10 treatments. In those patients with ANCA associated crescentic GN and severe renal failure at presentation, plasmapheresis along with immunosuppressive therapy have been used, with some success.

Renal Cortical Necrosis

RCN is a rare cause of ARF secondary to ischemic necrosis of the renal cortex and accounts for less than 2 percent of all cases of ARF in developed countries. The lesions are usually caused by significantly diminished renal arterial perfusion secondary to vascular spasm, microvascular injury or intravascular coagulation. RCN is usually extensive and bilateral, although focal and localized forms may occur, there is global necrosis of all the elements in the involved area of the cortex, including blood vessels, glomeruli and tubules. Irreversible loss of kidney function is the rule in complete cortical necrosis but is variable in the incomplete (patchy) type where less than 50 percent of nephrons are necrotic. The clinical course and outcome of patients with cortical necrosis can be classified into five broad groups (Table 7). Obstetric complications are the commonest (50 to 70 percent) cause of renal cortical necrosis, nonobstetric causes accounts for 20 to 30 percent of all cases of cortical necrosis and in these circumstance the incidence is higher in men than in women. The nonobstetric conditions leading to acute cortical necrosis are : extensive burn, pancreatitis, sepsis, snake bite, hemolytic uremic syndrome, hyperacute renal graft rejection and diabetic ketoacidosis. Septic abortion, abruptio placentae, postpartum hemorrhage, eclampsia, postpartum hemolytic uremic syndrome (HUS) and puerperal sepsis are the pregnancy-related situations responsible for renal cortical necrosis.

RCN accounts for 15 to 20 percent of all cases of ARF during the third trimester of pregnancy in developed nation. We observed that the incidence of RCN ranges from 10 to 30 percent of all cases of obstetric ARF. The incidence of RCN in obstetric ARF declined from 17 percent in 1982 to 1991 to 2.4 percent in 1992 to 2002. In our recent publication, RCN was noted in 2 out of 58 cases (3.4 percent) of obstetrical ARF in late pregnancy. Comparing our data of ARF in two periods (i.e., 1984 to 1994 and 1995 to 2005), the incidence of RCN in 1984 to 1994 was 6.7 percent of all cases of ARF which decreased to 1.6 percent in the 1995 to 2005 periods. Mortality decreased from 72 percent in 1984 to 1994 to 19 percent in 1995 to 2005. The observed differences in two study periods, 1984 to 1994 vs. 1995 to 2005, in relation to the incidence of obstetric ARF and RCN; mortality and outcome of patients with RCN; were statistically significant (Table 8). Renal biopsy is the gold standard for confirming the diagnosis of renal cortical necrosis. However, in

Table 7. Renal cortical necrosis: clinical course

1. Death in uremia during the acute phase
2. Survival without dialysis
3. Late return to dialysis/transplantation
4. Survival only with chronic maintenance dialysis/transplantation
5. Late resumption of sufficient renal function to become dialysis independent

recent years CT scan has emerged as a good noninvasive modality for early diagnosis of RCN. The characteristic finding is the presence of hypoattenuated subcapsular rim of renal cortex following contrast injection. Detection of cortical tram-track or egg-shell calcification on plain X-ray of abdomen or ultrasonography is helpful but is seen in only a minority. However, a noncontrast CT scan is more sensitive in picking up the cortical calcification.

ARF IN SPECIFIC SITUATIONS

This article will discuss ARF in: (a) Multiple Myeloma; (b) Pregnancy; and (c) Liver disease.

Myeloma-related Acute Renal Failure (M-ARF)

Multiple myeloma (MM) is a diffuse neoplasm of bone marrow plasma cells that produce several diverse effects on kidneys. The spectrum of renal diseases in MM include; ARF, chronic renal failure, nephrotic syndrome, Fanconi syndrome and amyloidosis. Light chain proximal tubulopathy and myeloma cast nephropathy typically present as Fanconi syndrome and ARF, respectively. We observed that ARF was the most common (52 percent) renal disease associated with multiple myeloma. ARF occurring in MM is often considered as irreversible and an ominous complication. Significant renal failure is found in about 75 percent of patients at the time of diagnosis of MM. Renal failure develops in an additional 25 percent of patients later in the course of MM. Thus, multiple myeloma is detected concomitantly with severe renal failure in 70 to 90 percent of patients. Light chain nephrotoxicity is considered as an important mechanism of ARF. Precipitating factors for ARF are hypercalcemia, dehydration, hypotension, infection and nephrotoxic drugs, such as NSAIDs. Hypercalcemia is a major precipitating factor for ARF, observed in 19 to 44 percent of patients in different series. Hypercalcemia predisposes to ARF by volume depletion as a result of emesis and by inducing nephrogenic diabetes insipidus. Volume depletion may enhance light chain nephrotoxicity and aggregation of light chain with Tamm-Horsfall protein in the kidneys. In most series of MM and ARF, there is a clear preponderance of light chain myeloma, with frequency ranging from 20 percent to 62 percent. We observed Bence Jones (BJ) proteinuria in 78 percent of patients. BJ protein represents light chain and is a probable cause of nephrotoxicity, resulting in ARF.

The mechanism of renal damage by light chains is controversial. There was no relationship between the light chain isoelectric point and nephrotoxicity. It has been suggested that unidentified light chain immunochemical properties are involved in the pathogenesis of cast formation and renal damage. Light chain can cause renal failure, even before other symptoms of MM manifest.

Table 8. Comparative data: Incidence and outcome of patients with renal cortical necrosis of all cases of acute renal failure in two 11-year periods; 1984-1994 and 1995-2005

Parameters	*Study period*				*Statistical analysis*	
	1984-1994 (n=536)		*1995-2005 (n=1286)*		*Z value*	*P Value*
	No	*%*	*No*	*%*		
Total ARF cases	536	-	1286	-	-	-
Obstetric ARF	76	14.0	134	10.4	2.17	<0.05
Total number of renal cortical necrosis (RCN)	36	6.7	21	1.6	4.77	<0.001
Obstetric RCN	25	4.7	7	0.5	4.41	<0.01
Non-obstetric RCN	11	2.0	14	1.0	1.42	>0.05
Outcome of RCN	(n=36)		(n=21)		Chi square test*	p-value
Mortality	26	72.0	4	19.0	12.99	<0.001
Progression to ESRD	6	16.6	10	47.6	4.85	>0.05
Partial recovery of renal function	4	11.11	7	33.33	2.90	>0.08

* With continuity correction factor. J Prakash, NDT 2007; 22: 1213-7.

However, there are patients who do not develop renal failure even though their urinary light chain excretion is extremely high. From an archive of 4,296 kidney biopsy specimens, 8 cases of light chain mediated acute tubulointerstitial nephritis were identified. All patients presented with ARF. Light microscopy revealed AIN. Immunofluorescence and electron microscopy failed to show definite evidence of light chain deposition along tubular basement membrane. However, ultrastructural immunogold labeling aided the demonstration of monotypical light chain along the tubular basement membrane. Thus, the accumulation of light chains along tubular basement membrane may induce an interstitial process that mimics acute tubulointerstitial nephritis. The treatment of M-ARF includes (i) Chemotherapy for reducing production of light chain; (ii) Intensive and prolonged dialysis and (iii) Rapid removal of light chain with plasmapheresis. The data on the reversibility of renal failure in multiple myeloma is also controversial, with reversibility rate ranging from 0 percent to 82 percent. Recovery of renal function is low in patients who received dialysis treatment. Renal function rarely recovers after four months on dialysis. However, very delayed partial recovery of renal function after 13 and 14 months on dialysis has been reported. Therefore, dialysis treatment along with chemotherapy should be continued for several months.

Regarding chemotherapy, it has been suggested that a rapid removal of light chain with chemotherapy and plasmapheresis could prevent irreversible renal failure. A small clinical trial compared forced diuresis and chemotherapy *versus* forced diuresis, chemotherapy and plasmapheresis. In terms of reversibility, there was slight trend in favor of the plasmapheresis group, but the difference was not statistically significant. Systemic chemotherapy reduces the production of light chains by eliminating the myeloma cells responsible for their production. Chemotherapy consisting of melphalan-prednisolone or VAD (vincristine, adriamycin and dexamethasone) regimen is the mainstay of treatment in myeloma associated kidney failure. Some investigators have shown that main prognostic indicators were prompted by renal histology. Recovery of renal function was found only in patients with typical cast nephropathy and/or tubular necrosis in the absence of interstitial disease. Global tubular atrophy and interstitial fibrosis are associated with partial or no recovery of renal function. High serum creatinine level was quoted as a marker of poor prognosis in a few studies. This implies that renal function impairment of any degree should be treated as a medical emergency. The timing of ARF in multiple myeloma influences the prognosis. The prognosis is worse who develop renal failure during chemotherapy.

In summary, ARF is the most common renal complication of multiple myeloma. MM should always be considered in differential diagnosis of unexplained ARF in adult and elderly persons. Recovery of renal function is achieved with dialysis and chemotherapy. Therefore, dialysis treatment along with chemotherapy should be continued for several months for better outcome of renal function.

Pregnancy-associated Acute Renal Failure (PR-ARF)

ARF has become a rare complication of pregnancy in developed countries. PR-ARF usually occurs in women with previously healthy kidneys. Despite converging trends, there are still huge differences in the incidence, causes and outcome of PR-ARF in developing countries compared with developed countries. This is closely linked to environmental and socioeconomic conditions. With the liberalization of abortion laws and improved obstetric care resulting in a decrease in septic abortion and the improvement of prenatal care in developed countries, PR-ARF is now an uncommon occurrence. Since 1960s, the incidence of PR-ARF has decreased from 1/3,000 to 1/15,000 to 1/20,000 with respect to the total number of pregnancies. Similarly, the proportion of PR-ARF from total cases of ARF has fallen from 20 to 40 percent in the 1960s to 0 to 1 percent in the last decade. In developing countries such as India, PR-ARF still accounts for 5 to 20 percent of total cases of ARF. However, prognosis has improved as indicated by decreased mortality (from 70 percent in 1984-1994 to 10 to 35 percent in 1995-2005). In a recent study from India, ARF complicated 1.78 percent of total deliveries. In contrast to extremely low (1 in 20,000 births) incidence of ARF in developed countries, ARF due to late obstetrical complication is still very high (1 in 56 births) in developing countries.

In developing countries the most common contributing factors to PR-ARF are abruptio placentae, puerperal sepsis, postpartum hemorrhage and septic abortion, whereas in developed countries the most common causes of PR-ARF are pre-eclampsia/eclampsia, thrombotic microangiopathy, sepsis and hemorrhage by abruptio placentae. Despite decreasing incidence, PR-ARF remains a serious complication with 10 to 30 percent of patients progressing to end-stage renal disease. The causes of PR-ARF are listed in Table 9. The presence of thrombotic microangiopathy and ARF in pregnancy is one of the most challenging differential diagnoses. Five pregnancy syndromes share many clinical, laboratory and pathological features: Preeclampsia/hemolysis elevated liver enzyme low platelet count (HELLP syndrome), thrombotic thrombocytopenic purpura (TTP)/HUS, acute fatty liver of pregnancy (AFLP), SLE with the antiphospholipid syndrome and disseminated intravascular coagulation (usually complicating sepsis). Although, it is difficult to establish clinical distinctions between these entities with certainty, the confluence of clinical and laboratory parameters can often establish a likely diagnosis (Table 10).

Preeclampsia/HELLP Syndrome

ARF is a rare complication of preeclampsia and is most frequently seen in the setting of severe preeclampsia, HELLP syndrome, coagulopathy, hepatic rupture or preexisting renal diseases. When ARF occurs in the setting of preeclampsia, termination of pregnancy is urgently indicated.

Acute Fatty Liver of Pregnancy

AFLP is a rare but potentially fatal complication of pregnancy, affecting about 1 in 10,000 pregnancies, with a 10 percent case fatality rate. The clinical picture is dominated by liver failure, with elevated serum aminotransferase levels and hyperbilirubinemia. Preeclampsia can also be present in up to half of the cases. Hemolysis and thrombocytopenia are not prominent features, and the presence of these findings should suggest the diagnosis of HELLP syndrome or HUS/TTP (Table 10). ARF in association with AFLP is seen mainly near term but can occur any time after midgestation. The cause of ARF in AFLP is obscure. It may be due to hemodynamic changes similar to that of hepatorenal syndrome or to a thrombotic microangiopathy. Management of AFLP includes, supportive care comprising aggressive management of the coagulopathy and prompt termination of the pregnancy. The syndrome typically remits postpartum with no residual hepatic or renal impairment, although it can recur in subsequent pregnancies.

Table 9. Causes of pregnancy-related acute renal failure (PR-ARF)

Sepsis-associated ARF
Septic abortion
Puerperal sepsis
Chorioamnionitis
Endomyometritis
Pyelonephritis
Pregnancy specific disorder
Preeclampsia/Eclampsia/HELLP syndrome
Pregnancy associated TTP
Pregnancy associated HUS
Acute Fatty Liver of Pregnancy (AFLP)
Obstetric complications
Amniotic fluid embolism
Antepartum hemorrhage (Abruptio placentae)
Postpartum hemorrhage
Enlarged gravid uterus

HELLP syndrome: Hemolysis elevated liver enzyme low platelet count;
TTP: Thrombotic thrombocytopenic purpura; HUS: hemolytic uremic syndrome.

Table 10. Comparison of clinical and laboratory characteristic of HELLP, TTP/HUS and AFLP

Clinical Features	*HUS/TTP*	*Preeclampsia/ HELLP*	*AFLP*
Hemolytic anemia	+++	++	±
Thrombocytopenia	+++	++	±
Coagulopathy	-	±	±
CNS symptoms	++	±	±
Liver diseases	±	+++	+++
Renal failure	++	+	++
Hypertension	±	++	±
Proteinuria	±	++	±
Elevated AST	±	++	++
Elevated bilirubin	++	+	++
Ammonia	Normal	Normal	High
Effect of delivery on diseases	None	Recovery	Recovery
Management	Plasma Exchange	Supportive care, delivery	Supportive care, delivery

Hemolytic-Uremic Syndrome/Thrombotic Thrombocytopenic Purpura

It is characterized by thrombocytopenia, hemolytic anemia and variable organ dysfunction including ARF. Patients are believed to have TTP, when neurological symptoms dominate; and HUS, when renal failure is the dominant presenting feature. Pregnancy appears to be associated with an increased risk of both TTP (usually presenting prior to 24 weeks) and HUS (typically occurring near term or postpartum). Pregnancy can precipitate relapse in women with a history of TTP. Increasing concentration of pro-coagulant factors, decreased fibrinolytic activity, loss of endothelial cell thrombomodulin, and decreasing activity of plasma metalloprotease (ADAMTS 13) may contribute to development of TTP/HUS in susceptible individuals. The often challenging clinical distinction between HUS/TTP and preeclampsis/HELLP is important for patient management, because plasma exchange is beneficial in HUS/TTP but not in HELLP syndrome. A history of preceding proteinuria, hypertension and severe liver injury is more suggestive of the HELLP syndrome; whereas the presence of renal failure, severe hemolytic anemia and isolated elevation of LDH are more typical for HUS/TTP (Table 10). Similar to nonpregnant patients, plasma exchange is the essential therapy for TTP/HUS and it is safe and effective. Termination of pregnancy does not appear to alter the course of HUS/TTP; thus, it is not generally recommended unless the fetus is compromised. Women who develop HUS/TTP should be aware of the potential for relapse as well as of the risk of relapse in subsequent pregnancies.

SLE and Antiphospholipid Syndrome

Patients with SLE and associated antiphospholipid antibodies are at risk for tissue ischemia, secondary to thromboembolic events and thrombotic microangiopathy resembling HELLP syndrome and HUS/TTP. Patients with renal involvement, hypertension and proteinuria, have identical picture as patients with preeclampsia. However, management of the SLE flare will differ from the management of preeclampsia. Prednisolone is used in patients with lupus nephritis, whereas combined regimen of prednisolone and low dose aspirin are recommended in patients with antiphospholipid antibodies. Patients with catastrophic antiphospholipid syndrome should be treated with full anticoagulation with heparin and steroids plus plasma exchange.

Acute Renal Failure in Liver Disease

ARF is relatively frequent problem, occurring in approximately 20 percent of hospitalized patients with cirrhosis of liver. The differential diagnosis of ARF in association with liver disease includes: (i) Pre-renal azotemia (due to decreased effective circulatory volume); (ii) ATN and (iii) hepatorenal syndrome. Pre-renal ARF results from volume depletion, hypoalbuminemia, splanchnic vasodilation, gastrointestinal hemorrhage and diuretics. Severe renal hypoperfusion (gastrointestinal hemorrhage, sepsis, nephrotoxic drug and rapid paracentesis) leads to ATN. The most common cause of ARF in cirrhotic patients is pre-renal AKI accounting for approximately 68 percent of the cases. ATN and hepatorenal syndrome (HRS) accounts for about 30 percent and 17 percent of the cases of ARF respectively in patients with cirrhosis of liver. Drug induced tubulointerstitial nephritis (diuretics, sulfonamide, phenytoin) and glomerulonephritis/vasculitis in association with HCV/HBV infection are another uncommon causes of ARF in patients with liver diseases. Abdominal Compartment Syndrome (ACS) due to tense ascites and increased intra-abdominal pressure (>20 mmHg) can cause ARF in cirrhotic patients. Reduction of intra-abdominal pressure after paracentesis improves kidney function. The HRS is a functional renal failure characterized by renal vasoconstriction in patients who have advanced acute or chronic liver disease. Based on the speed of onset of renal failure, two forms of HRS can be distinguished:

- Type I HRS is defined as at least 50 percent decrease of the creatinine clearance or at least a twofold increase in serum creatinine to a level higher than 2.5 mg/dL in less than two-week period. This type of HRS presents as ARF, usually following precipitating event.
- Type II HRS is defined as a more gradual development of renal failure, mostly developing over weeks to months. The typical clinical pattern of HRS Type II is refractory ascites. Both types of HRS are often present in the same patient. Elevated serum creatinine (HRS Type II) is a frequent finding in patients with advanced liver disease. These patients are susceptible to a rapidly progressive reduction of renal function (HRS Type I) when a precipitating event occurs. A typical course of a patient with HRS is shown in (Fig. 3).

HRS is not a rare disease. About 39 percent of cirrhotic patients develop HRS at five years. Once established, the prognosis for untreated HRS is extremely poor. In patients without liver transplantation, the median survival time for HRS Type I has been calculated to be two weeks and for Type II six months. It should be kept in mind that significant renal insufficiency may be present despite normal serum creatinine and serum urea, because these patients are frequently malnourished with a reduced muscle mass and low urea production rate due to liver disease. International Ascites Club published revised diagnostic criteria for HRS in 2007 (Table 11). Specific therapies of ARF depend on the most likely causes are known for HRS. Vasoconstrictors are useful bridging therapy in HRS. Ultimately liver transplantation is indicated in otherwise reasonable candidates in whom ARF does not resolve.

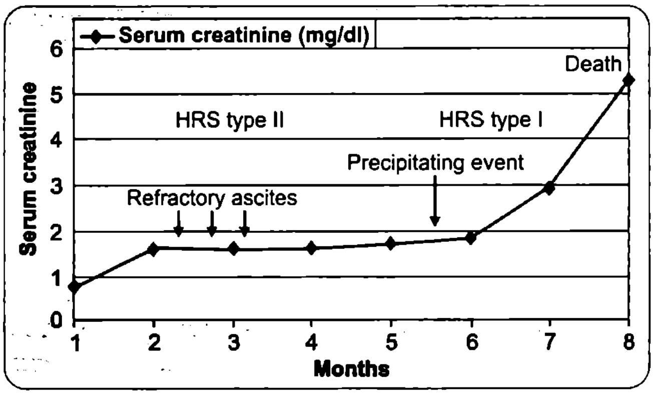

Figure 3: Typical clinical course of a patient with cirrhosis and progressive renal failure

Table 11. New international ascites club's diagnostic criteria for HRS

- Cirrhosis with ascites
- Serum creatinine > 1.5 mg/dL
- No improvement In serum creatinine after at least 2 days with diuretic withdrawal and volume expansion with albumin. The recommended dose of albumin is 1 gm/kg of body weight per day upto maximum of 100 gm/day.
- Absence of shock
- No current or recent treatment with nephrotoxic drugs
- Absence of parenchymal kidney disease as indicated by proteinuria > 500 mg/day, microhematuria and/or abnormal renal ultrasonography

KEY POINTS

1. Sustained prerenal azotemia is the most common cause of ischemia-induced ATN.
2. Primary (intrinsic) renal diseases that result in ARF are categorized according to the site of injury: tubules, interstitium vessels or glomerulus. The major cause of intrinsic ARF is ATN.
3. Drug-induced disease is the most common (60 to 70 percent) etiology of AIN.
4. AGN accounts for approximately 9 percent of total cases of ARF.
5. Systemic vasculitis accounts for only a small minority of cases of ARF (5 percent).
6. Corticosteroid in combination with cyclophosphamide remains the mainstay of therapy for crescentic glomerulonephritis.
7. Pulmonary hemorrhage is the definite indication of plasmapheresis in patients with anti-GBM diseases and Pauci-immune vasculitis.
8. PR-ARF still accounts for 5 to 20 percent of total cases of ARF in developing countries.
9. Renal cortical necrosis accounts for less than 2 percent of all cases of ARF in adult and obstetrical complications are the most common cause of RCN.
10. ARF is the most common myeloma-associated renal disease.
11. ARF occurs in approximately 20 percent of patients with cirrhosis of liver and prerenal factors accounts for 70 percent of all cases of ARF in liver cirrhosis.

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A Reversible Syndrome of Acute Renal Failure Associated with Renin-Angiotensin Inhibitor Drugs

Anil K Mandal

The content of this chapter is reproduced in part from the previously published articles.

INTRODUCTION AND CASE REPORTS

A reversible syndrome of acute renal failure (ARF) was described in patients with bilateral renal artery stenosis (RAS) or solitary kidney RAS treated with angiotensin converting enzyme inhibitors (ACEI) drugs in the past. This reversible ARF associated with ACEI has also been described in unilateral RAS, and in parenchymal renal diseases with no evidence of RAS. In addition to ACEI drugs, angiotensin receptor blocking (ARB) drugs were later on added to renin-angiotensin inhibitor armamentarium. Over the years, these two groups of drugs have been used like potatoes in any illness associated with proteinuria or impaired renal function, including hypertension, diabetes or congestive heart failure as a renoprotective therapy. Physicians are highly influenced by pharmaceutical companies and clinical trials to prescribe these drugs in an unabated fashion to prevent end stage renal disease (ESRD) going into dialysis. As these drugs are used in an unabated fashion, more and more patients are entering into the emergency room of hospitals when they are found to have ARF.

An easy excuse is developed to blame RAS as the cause of ARF associated with ACEI/ARB drugs. But RAS is not found in most patients. Here is an example. A 46-year-old African-American female, full-time employee, was admitted to a hospital on December 30, 2001, with the complaint of nausea, vomiting, dizziness, and low urine output. She was found to have ARF. On September 27, 2001, her primary care physician prescribed a combination of lisinopril and hydrochlorothiazide for control of hypertension. Laboratory on July 10, 2001, was normal. On December 30, 2001, at the emergency room her laboratory showed BUN 67 mg/dL, serum creatinine 5.6 mg/dL, sodium 130 mmol/L, potassium 4.5 mmol/L, chloride 97 mmol/L, CO_2 19 mmol/L, glucose 103 mg/dL, hemoglobin 10.9 g/dL. Lisinopril and hydrochlorothiazide were discontinued, and she was treated with normal saline infusion at 60 ml/h. Two days later, on January 1, 2002, laboratory showed BUN 32 mg/dL, serum creatinine 1.5 mg/dL, normal electrolytes, CO_2 19 mmol/L, and hemoglobin 10.5 g/dL. Normal saline infusion was discontinued. She was discharged from the hospital. At a follow-up office visit on February 28, 2002, her laboratory values were all normal. Her hemoglobin increased to 12.7 g/dL. She did not receive exogenous erythropoietin.

Comment

This patient had documented normal renal function five months prior to development of ARF. She was not taking any other medicine except HCTZ and lisinopril, which caused her ARF. HCTZ caused hyponatremia Na+ 130 mmol/L. Serum K was normal because of HCTZ. Reversal of ARF to normal renal function after withdrawal of lisinopril indicates that ARF was caused by lisinopril. Mild volume depletion caused by HCTZ adds to low BP produced by ACEI, resulting in rapidly decreased renal perfusion and rapid onset of ARF. The rapid recovery of renal function assisted by fluid therapy associated with increase in BP and, hence, increase in renal function.

Adapted in part from Mandal AK, Hiebert LM. *Clin Nephrol* 2008;69:169-78. This patient developed chest pain soon after discharge from the hospital. She underwent cardiac catheterization and coronary arteriogram to rule out coronary artery disease. Coronary arteries showed no obstruction. Renal arteriogram done during the procedure showed normal renal arteries.

Here is another patient with uncontrolled diabetes who developed the typical syndrome of reversible ARF, hyperkalemia and metabolic acidosis.

A 59-year-old African-American male with a long history of diabetes was admitted to a hospital with diagnosis of ARF, hyperkalemia and metabolic acidosis. He was taking lisinopril (ACEI) 20 mg orally daily. Lisinopril was discontinued and he was treated with insulin and infusion of normal saline with sodium bicarbonate. His glucose control improved, and renal function returned to normal as did the electrolytes and acid-base balance (Table 1).

Here is another patient with very long history of diabetes who developed ARF with ACEI, accupril. Discontinuation of accupril resulted in rapid decrease of BUN and serum creatinine levels. This patient illustrates that uncontrolled severe hyperglycemia in and of itself causes slight deterioration of renal function but renal function improves with control of hyperglycemia (Table 2). ***Therefore, the main causes of renal function deterioration or doubling of serum creatinine or going into dialysis in diabetes is the use of ACEI or ARB or a combination of both.***

Here is an example showing substantial decrease of creatinine clearance (Ccl) by 56 percent associated with 27 percent increase of serum creatinine (Table 3). Although 27 percent increase in serum creatinine is noted, at a glance, changes in serum creatinine levels between 1999 and 2004 seem unconvincing. This is exactly what has led to the unfortunate publicity of renal protection by ACEI/ARB drugs. In almost all or all cases, renal clearance (Ccl or iothalamate clearance) either was not done or not reported. Therefore, reduction of proteinuria with use of ACEI or ARB therapy is secondary to reduction of renal clearance as is clearly seen in Table 3.

Mechanism underlying reduction of proteinuria with use of ACEI/ARB has not been defined. Reduction of intraglomerular pressure has been proposed which will reduce filtration of protein but only associated with simultaneous reduction of overall glomerular filtration rate. Unfortunately, this reduction of clearance is not easily detected by serum creatinine levels. In a situation of ARF associated with use of ACEI or ARB and a diuretic, frequently the diuretic is blamed for ARF and the recommendations are to discontinue diuretic, but continue ACEI or ARB as a renoprotective therapy. A patient is presented to reveal just the contrary.

Here is an example of a patient whose renal function continues to improve with discontinuation of ACEI/ARB, but with continuation of a potent diuretic, such as bumetanide. A 66-year-old African-American male, admitted to a hospital for shortness of breath from chronic obstructive pulmonary disease and swelling of legs, was seen in consultation by a nephrologist for renal failure.

Table 1. Serial laboratory studies in a 59-year-old African-American male with a long history of diabetes mellitus

Date	*Glucose (F)*	*BUN*	*SCr*	*Na$^+$*	*K$^+$*	*CO$_2$*
2005	*(mg/dl)*	*(mg/dl)*	*(mg/dl)*	*(mmol/L)*	*(mmol/L)*	*(mmol/L)*
Aug 18	302	76	7.4	126	5.9	15
Hospital admission: Lisinopril discontinued						
Aug 19	274	80	8.2	127	5.0	17 (pH 7.31, base excess -7.7)
Normal saline with 3 ampoules of sodium bicarbonate infusion started						
Aug 20	249	68	2.2	133	5.6	18
Aug 21	196	22	0.8	139	4.2	32
Aug 22	186	10	0.8	140	3.8	33
Discharged from hospital						

F-fasting, BUN–blood urea nitrogen, SCr–serum creatinine.

Adapted from Mandal AK, Hiebert LM. Clin Nephrol 2008;69:169-78.

Note that his kidney function is already reduced to chronic kidney disease (CKD) stage 3, and he is anemic (Table 4). Anemia is a common complication of ACEI/ARB, but not recognized intentionally or unintentionally. Nephrologist's impression was renal failure due to high uric acid causing uric acid nephropathy. Uric acid was 6 mg/dL (n=3.4 to 7 mg/dL) on August 10, 2009. He recommended to continue current therapy, including losartan, and considered addition of an ACE inhibitor. He didn't mention that ARF was due to losartan but permitted the patient to progress to severe renal failure. He told the patient that he would need dialysis soon. Patient refused dialysis.

Table 2. Serial laboratory studies in a 54-year-old white female with a history of diabetes mellitus for 52 years

DATE	*Glucose*	*BUN*	*SCr*	*Na^+*	*K^+*	*CO_2*	*Hb*	*Hct*
2003 - 2005	*(mg/dl)*	*(mg/dl)*	*(mg/dl)*	*(mmol/l)*	*(mmol/l)*	*(mmol/l)*	*(g/dl)*	*(%)*
May 29, 2003	139 (F)	71	2.4	137	4.3	33	NA	NA
May 29, 2003			Accupril discontinued					
July 07, 2003	95 (F)	21	1.2	143	4.2	27	11.9	36.4
Nov 28, 2003	115	32	1.2	136	3.6	23	12.6	36
Dec 31, 2003	>503 (A)							
			Hospital Admission					
Jan 01, 2004	>600 (A)	49	1.9	135	4.0	30	11.6	36.2
Oct 08, 2004	205 (F)	32	1.5	135	4.0	23	NA	NA
Jan 05, 2005	133 (F)	43	2.1	141	4.7	21	10.1	30.4
Apr 28, 2005	167 (F)	23	1.1	140	4.4	24	13.9*	42.7*
Nov 7, 2005	203 (F)	26	1.2	145	4.3	26	13.2*	38.3*

* Received no exogenous erythropoietin (epogen, procrit or darbepoetin)

F = fasting, A = Accucheck, BUN = blood urea nitrogen, SCr = serum creatinine, Hb = hemoglobin, Hct = hematocrit, NA = not available.

Adapted from Mandal AK, Hiebert LM. Clin Nephrol 2008;69:169-78.

Table 3. Effect of fosinopril on proteinuria and renal function in a 67-year-old African-American female with a history of diabetes for 12 years

Date	*24h Proteinuria*	*24h Ccl*	*Serum Creatinine*
1999 - 2006	*(mg)*	*(ml/min)*	*(mg/dl)*
Oct 17, 1999	160	125	0.8
	Fosinopril 20 mg daily started		
Nov 09, 2000	88	90	0.9
Dec 08, 2002	142	81	1.0
Feb 18, 2004	5	55	1.1
	Fosinopril discontinued. Referred for decreased Ccl		
July 15, 2004	151	96	1.0
Jan 20, 2005	417	76	1.0
Apr 07, 2005	215	86	0.9
Jun 08, 2006	257	70	0.7
Dec 11, 2006	<150	80	0.96

CcL = creatinine clearance

Adapted from Mandal AK, Hiebert LM. Clin Nephrol 2008;69:169-78.

The primary care physician cancelled this nephrology consultation and referred him to the author. Here are serial laboratory reports of this patient (Tables 4 and 5).

This patient was followed by the author from August 18, 2009. Furosemide and losartan were discontinued as of August 18. He was later on placed on a loop diuretic, bumetanide (Bumex®) 1 mg orally daily, for edema of both legs. But renal function continued to improve despite use of bumetanide (Table 5).

His total kidney function plunged to 14 ml/min eGFR (normally >60 ml/min) on August 18.

After discontinuation of losartan but with continuation of a diuretic, his renal function continues to improve. eGFR increased to 52 ml/min, and hemoglobin increased to 13 g/dL. He feels very well and happy.

Progressive renal failure in this patient and other previous patients is a compelling evidence that ACEI/ARB make the patients a prey of dialysis. This patient surely would have gone to dialysis if he was not transferred to the care of the author.

Results

An analysis of 12 patients treated with ACEI/ARB is presented. The youngest patient in this series was 46 years and the oldest was 90 years. Mean age of the total 12 patients was 65.6 years. Six were males and six females. Six had diabetes (50 percent), four of them also had hypertension; three had hypertension but no diabetes, and one each had history of urinary tract infection and CHF. Eight patients (67 percent) received ACEI (lisinopril); four patients (33 percent) received ARB (losartan, irbesartan, telmisartan). Ten patients concomitantly received diuretic(s) (furosemide, hydrochlorothiazide, metolazone, bumetanide) (83 percent). The laboratory results before (pre), during (upon admission), and after discontinuance (post) of ACEI and ARB therapy in 1 to 10 patients can be found at a glance in Table 6: Renal Function Parameters, Electrolytes, and Hemoglobin Before, During, and After Discontinuation. Wherever available, pre eGFR was normal or slightly reduced. During admission, BUN and

Table 4. Initial laboratory results from a 66-year-old African-American male treated with a combination of ARB, losartan, and furosemide who developed acute renal failure

Normal Range	*August 2009 Dates*	*10th*	*11th*	*12th*	*14th*	*17th*	*18th*
6 - 19	BUN (mg/dL)	21	21	20	21	34	37
0.8 - 1.5	SCr (mg/dL)	1.92	2.02	1.96	2.69	3.36	4.15
> 60	eGFR (ml/min)	37	35	37	25	20	15
3.5 - 5.0	Serum K (mmol/L)	4.2	4.0	3.9	4.0	3.9	3.7
24 - 34	Serum CO_2 (mmol/L)	28	31	31	32	35	35
13.5 - 18	Hemoglobin (g/dL)	12.9	11.4	NA	11.9	11.5	NA
SCr, Serum Creatinine; eGFR, estimated Glomerular Filtration Rate; K, serum potassium; NA, not available.							

Table 5. Laboratory results from a 66-year-old African-American male after discontinuation of ARB, losartan but continued with bumetanide and showing recovery from acute renal failure

Normal Range	*6 – 19*	*0.8 – 1.5*	*> 60*	*3.5 – 5.0*	*24 – 34*	*13.5 – 18*	
Lab Panel No	*BUN*	*SCr*	*eGFR*	*Serum K*	*Serum CO_2*	*Hemoglobin*	*Uric*
Losartan	*(mg/dL)*	*(mg/dL)*	*(ml/min)*	*(mmol/L)*	*(mmol/L)*	*(g/dL)*	*Acid*
19 Aug '09	44	4.51	16.9				
20 Aug '09	43	3.81	17				
21 Aug '09	38	3.04	22				
8 Sep '09	12	1.86	39	3.9	28	12.9	5.1
6 Oct '09	17	1.65	45	3.9	27	13.0	
3 Dec '09	15	1.30	59	4.1	29	13.9	5.8
17 Feb '10	14	1.44	52	4.0	29	12.9	
SCr = serum creatinine; eGFR = estimated glomerular filtration rate; K = serum potassium.							

Table 6. Renal function parameters, electrolytes, and hemoglobin before (pre), during (upon admission), and after discontinuation (post)*

Patient		*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
Age, Race, Gender		*51 WM*	*51 WF*	*46 AAF*	*59 AAM*	*75 WM*	*47 WM*	*67 AAF*	*70 WM*	*88 AAF*	*90 WF*
Diagnosis		Diabetes, Hypertension	CHF	Hypertension	Diabetes	Diabetes, Hypertension	Chrohn's disease, Diabetes	Diabetes, Hypertension, COPD	Hypertension	Diabetes	Urinary Infection
ACEI, ARB, Diuretic		Lisinopril, HCTZ	Lisinopril	Lisinopril, HCTZ	Lisinopril	Lisinopril, Furosemide	Lisinopril, Furosemide	Irbesartan, Furosemide, Metolazone	Irbesartan, Furosemide	Lisinopril, Furosemide	Telmisartan, Losartan, Furosemide
BUN/SCr (mg/dL)	Pre	NA	NA	11/0.8 99.3	NA	33/1.9 36.9	15/0.6 153.4	35/2.6 23.6	NA	31/1.5 42.1	NA
eGFR (ml/min)	During	71/6.3 10	97/4.0 12.5	67/5.6 14.1	76/7.4 9.8	128/3.9 16.0	52/2.2 32.2	86/5.8 9.3	71/3.1 21.2	78/2.9 19.6	80/2.6 18.3
	Post	24/1.0 83.7	22/0.9 118	16/0.9 86.6	22/0.8 127.2	68/1.8 39.2	32/1.0 85.1	36/2.8 21.6	21/1.3 58	27/1.2 54.5	38/1.6 32.1
CO_2 (mmol/L)	Pre	NA	NA	23	NA	NA	NA	30	NA	28	NA
	During	17.1	16	19	15	19	19	35	20	24	15
	Post	24	24	24	33	20	26	27	24	21	29
Hb (g/dL)	Pre	NA		11.9	NA	NA	13.7	NA	NA	NA	
	During	10.9	14.6	10.9	NA	8.4	10.6	NA	12.8	11.5	11.9
	Post	10.7	NA	12.9	NA	9.3	NA	NA	11.1	10.3	11.6

Hb = hemoglobin.

SCr: serum creatinine, HCTZ: hydrochlorothiazide, NA: not applicable serum creatinine were uniformly elevated, and eGFR or Ccl was uniformly reduced. Initial eGFR/Ccl was less than 20 ml/min in nine patients (82 percent). In a matter of a few days, after discontinuance of ACEI/ARB therapy and with fluid therapy, eGFR reached normal (>60 ml/min) in 5 of 10 patients (50 percent). Estimated GFR increased to near normal in three patients. In two patients, eGFR recovered to baseline. Fifty percent of the patients had hyperkalemia, and 75 percent of the patients had metabolic acidosis. Hyperkalemia and metabolic acidosis remitted after discontinuance of ACEI/ARB and with bicarbonate infusion. Seven patients (58 percent) had anemia, which improved with improvement of renal function and exogenous erythropoietin administration. Long-term follow up shows that renal function remains normal after recovery.

Overall Discussion

Author's studies affirm that ACEI/ARB group of drugs unequivocally cause reversible ARF. Further, these studies reveal that these drugs also cause hyperkalemia and metabolic acidosis in a majority of the patients. Discontinuation of these drugs and treatment with bicarbonate infusion and 9-alpha fluodrohydrocortisone (Florinef®) hasten recovery of renal function and cause reversal of hyperkalemia and metabolic acidosis. Exogenous erythropoietin accelerates correction of anemia in this syndrome. Bicarbonate infusion consists of half normal, normal saline or 5 percent dextrose in water with one to three ampoules of sodium bicarbonate (44.5 mmol of sodium bicarbonate per amouple) per liter bag. Bicarbonate content in the fluid depends on serum bicarbonate level and arterial pH. Preferred vehicle for bicarbonate infusion is 5 percent dextrose in water, if patient is not diabetic. Choice of half normal or normal saline depends on serum sodium level. The infusion rate is 50 to 60 ml/h. Usually the bicarbonate infusion runs for 72 to 96 hours, but in occasional patients infusion runs until renal function shows steady improvement.

By definition, all patients in these studies developed ARF usually heralded by the elevation of serum creatinine ≥0.5 mg/dL from the baseline. Although no consensus exists on definition of ARF, it is reasonable to define ARF as ≤2 week increase in serum creatinine of 0.5 mg/dL for patients with baseline serum creatinine of <2.5 mg/dL. Renal function can deteriorate soon after ACEI therapy is initiated, or in patients receiving chronic ACEI or ARB therapy, as shown in Figure 1.

Like the author, other investigators have noted increases in BUN and serum creatinine levels when an ACE inhibitor is used concomitantly with a diuretic, especially in the setting of CHF. In most reported cases, the severity of renal insufficiency was mild (0.3 mg/dl increase of serum creatinine from baseline) not requiring discontinuation of therapy. However, renal function decrease can be marked, as illustrated in this study (Figure 2) warranting discontinuation of ACE inhibitor therapy.

The mechanism of ACEI/ARB-induced ARF has not been fully elucidated. However, it is evident that volume depletion from concomitant diuretic therapy, as in most of the patients, or from osmotic diuresis, as in uncontrolled diabetes potentiates ACEI/ARB-induced ARF. Very low BP caused by ACEI/ARB is additive to volume depletion and decreased renal perfusion. Strong evidence for that is the fact that volume replacement in the form of normal saline or bicarbonate infusion hastens recovery from ARF.

Urinary sodium is low and urinary potassium is only slightly high even in the face of diuretic therapy in many patients treated with ACEI and a diuretic as shown in Table 7.

Table 7. Urinary electrolytes in patients treated with an ACE and a diuretic

No	*Date*	*Sodium (mEq/l)*	*Chloride (mEq/l)*	*Potassium (mEq/l)*
2	Feb 1, 93	72	36	34
3	Feb 9, 93	<5	17	43
4	Feb 6, 93	42	47	48
5	Feb 4, 93	18	19	45
6	Aug 9, 91	28	8	30
7	Nov 25, 91	22	18	35
After 24 hr saline infusion (100 ml/hr)				
3		17	26	27
5		36	32	37
6		16	24	34
7		89	151	186

Adapted from Mandal et al. Clin Nephrol 1994;42:170-4.

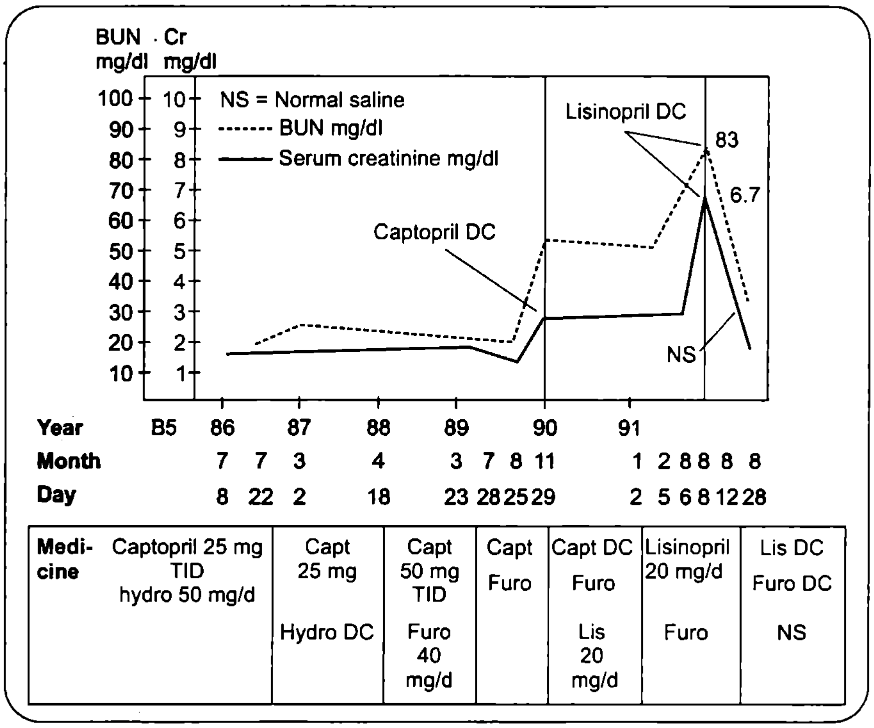

Figure 1: A 59-year-old white male had a long-standing history of uncontrolled hypertension. He was treated with a combination of captopril (CAPT) and hydrochlorothiazide (HYDRO) for almost 5 years with only slight change in BUN and serum creatinine (SCr). BUN and SCr started to increase when HYDRO was substituted by furosemide (FURO). Renal function deteriorated fast soon after CAPT was replaced by lisinopril (LIS). BUN and SCr returned to almost baseline rapidly upon discontinuation (DC) of both LIS and FURO and with normal saline infusion. Adapted from Mandal et al Clin Nephrol 1994;42:170-4

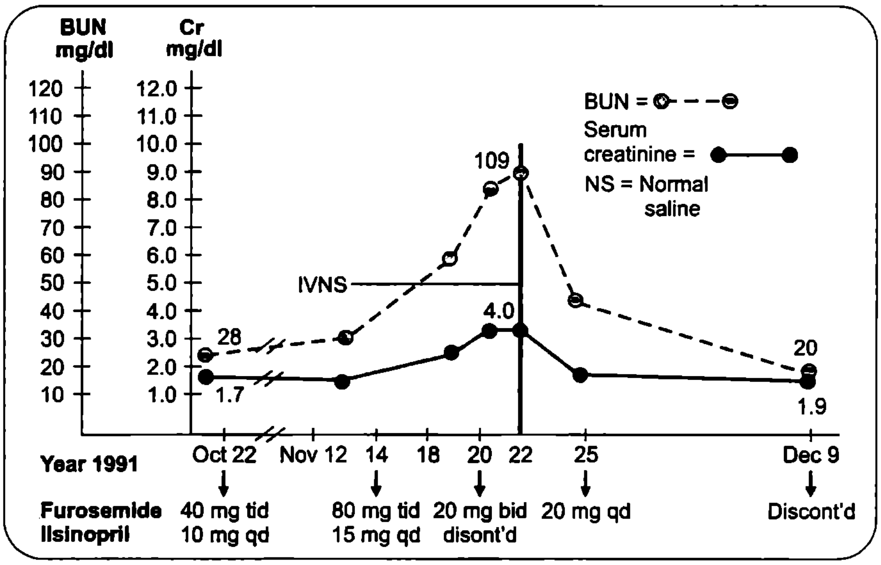

Figure 2: 75-year-old white male was admitted with a history of severe shortness of breath and swelling of the legs. Within 3 weeks of initiation of high dose of furosemide (240 mg/day) and lisinopril (15 mg/day), BUN and serum creatinine levels rapidly increased. BUN and serum creatinine levels decreased rapidly upon discontinuation of lisinopril, and with infusion of normal saline (NS). Furosemide was continued in a reduced dose until BUN and serum creatinine returned to baseline levels. Furosemide was then discontinued. Adapted from Mandal et al. Clin Nephrol 1994;42:170-4

The information in Table 7 is supportive of volume depletion as an important predisposing factor for ACEI-induced ARF. Because angiotensin II is necessary for maintenance of GFR during states of significant volume depletion and low blood pressure—such as uncontrolled diabetes, diuretic therapy, old age, chronic diarrhea, or vomiting—further suppression of angiotensin II with ACEI/ARB therapy can cause GFR to decline rapidly with consequent oliguric or anuric ARF. Continuation of diuretic therapy does not prevent recovery of renal function, however (Tables 4 and 5). Recurrence of renal function deterioration with reinstitution of ACEI/ARB, as in author's observation, is strong evidence that these drugs are directly related to ARF.

Bicarbonate infusion hastens recovery of eGFR faster than normal saline alone, if ARF is associated with metabolic acidosis, as shown in this author's reports.

Elderly subjects (>65 years) are likely to develop this syndrome. Mean age of this cohort was 65.6 years. Metabolic acidosis and hyperkalemia are, at least in part, due to hyporeninemia and hypoaldosteronism associated with diabetes and are further aggravated by the use of ACEI/ARB. It has been generally accepted that acidosis increases plasma potassium concentration primarily mediated via a shift in potassium between intracellular and extracellular compartments. Hence, bicarbonate infusion and use of 9-alpha fluodrohydrocortisone (aldosterone analog) hasten reversal of hyperkalemia and metabolic acidosis. Fluodrohydrocortisone (Florinef®) additionally promotes renal perfusion by the increase of blood pressure.

ARF in the intensive care settings is common and carries a high risk of mortality. There was no mortality observed in author's study population mainly due to prompt initiation of bicarbonate infusion. Hemodialysis is indicated in severe ARF associated with moderate to severe metabolic acidosis and hyperkalemia. However, low dose continuous bicarbonate infusion at a rate 50 to 60 ml/h for several days appears to be an effective substitute for hemodialysis for ACEI/ARB-induced ARF in the ICU settings, as shown in author's studies.

Moderate to severe hyperkalemia is a distinct threat making physicians to admit these patients in a critical care unit with escalating cost of health care as reported by other authors. The risk of hyperkalemia is much higher in diabetes than other medical conditions due to preexistent hyporeninemia and hypoaldosteronism. This risk is even higher, leading to life-threatening hyperkalemia, when ACEI is used in combination with spironolactone. However, concomitant high dose diuretic(s) therapy helps to mitigate hyperkalemia and metabolic acidosis.

KEY POINTS

1. Author's own studies and studies from other authors indicate that ACEI/ARB group of drugs cause reversible ARF.
2. ARF is most often associated with hyperkalemia, metabolic acidoses and anemia constituting a syndrome.
3. High risk for this syndrome includes those who are elderly (> 65 years); and those with uncontrolled diabetes, or dehydration from diarrhea, vomiting or diuretic therapy.
4. Detection at an early stage and discontinuation of ACEI/ARB drugs will restore renal function and reverse hyperkalemia and metabolic acidosis.
5. Infusion of normal saline or preferably bicarbonate solution hastens recovery of renal function and reversal of metabolic acidosis.
6. Fludrocortisone (Florine®) is an essential treatment for those with moderate to severe hyperkalemia.
7. Hemodialysis is seldom required to reverse ARF.

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Chronic Renal Failure: Clinical Perspective, Prevention, and Nondialysis Treatment

Anil K Mandal

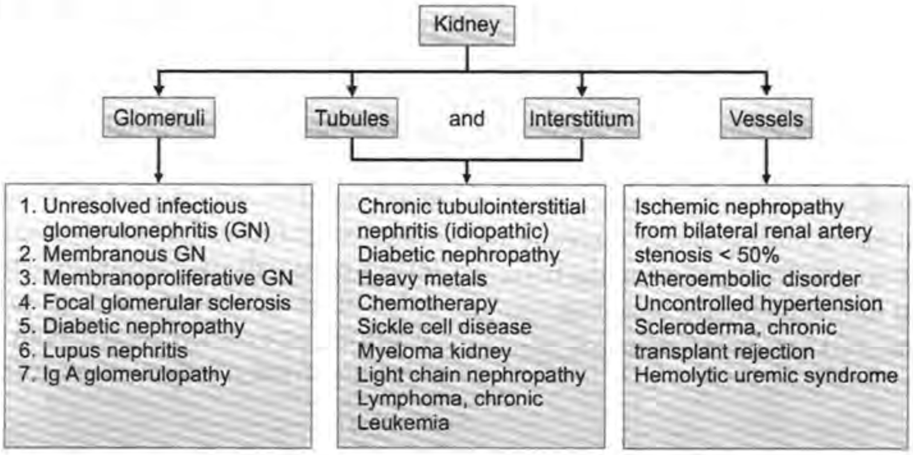
DEFINITION AND INTRODUCTION

Chronic renal failure (CRF) by definition is renal failure, which is generally progressive and nonreversible. Presently, the most common cause of CRF is diabetes-related renal disease. Fifty to 60 percent of CRF is of diabetic origin. Frequently, the term end stage renal disease (ESRD) is used for advanced CRF. In this chapter, the terms advanced CRF and ESRD may be used interchangeably. However, for the convenience of the readers, causes of CRF are presented in a schematic diagram.

Among the glomerular diseases, focal glomerular sclerosis is only second to diabetic nephropathy as a cause of CRF. Glomerular diseases, including membranous GN, membranoproliferative GN, are relatively uncommon causes of CRF in the United States. However, the spectrum may be different in Asia, Africa or Middle East, where unresolved infectious glomerulonephritis from streptococcal infection, hepatitis B and C and malaria are common causes of CRF. IgA nephritis is emerging as a common cause of CRF worldwide.

Less common causes of relentless renal failure include, light chain nephropathy, myeloma kidney, ischemic nephropathy from bilateral mild to moderate renal artery stenosis, atheroembolic disease of the kidney and chronic transplant rejection.

Glomerular filtration rate (GFR) is considered as the best overall indicator of renal function. GFR is measured most commonly in clinical practice by creatinine clearance (Ccl). In order to obtain an accurate Ccl, proper urine collection is important. Patient is instructed accordingly of the technique with example as shown below.


Kidney
Glomeruli
Tubules
and
Interstitium
Vessels
1. Unresolved infectious glomerulonephritis (GN)
2. Membranous GN
3. Membranoproliferative GN
4. Focal glomerular sclerosis
5. Diabetic nephropathy
6. Lupus nephritis
7. Ig A glomerulopathy
Chronic tubulointerstitial nephritis (idiopathic)
Diabetic nephropathy
Heavy metals
Chemotherapy
Sickle cell disease
Myeloma kidney
Light chain nephropathy
Lymphoma, chronic Leukemia
Ischemic nephropathy from bilateral renal artery stenosis < 50%
Atheroembolic disorder
Uncontrolled hypertension
Scleroderma, chronic transplant rejection
Hemolytic uremic syndrome

TECHNIQUE

1. 24-hour urine collection starts at the time the patient empties his or her bladder. This first void is not saved.
2. All urine voided throughout the next 24 hours is collected in a clean container.
3. The urine is either refrigerated or kept on ice.
4. The patient must empty the bladder at the end of the 24-hour urine-collection period. This urine is saved, and all urine is taken to the laboratory.

Example

1. Patient awakens at 8:00 am, urinates, and discards the urine.
2. Patient urinates at noon, at 4:00 pm, 8:00 pm, and at 11:00 pm. All urine is saved.
3. At 8:00 am the following day, the patient urinates. With the saving of this urine, the collection ends.

Calculation of 24-hour Ccl

Classic Formula: UV/P

U = Urine Creatinine in mg/dL

V = Volume of Urine in ml/min

P = Serum Creatinine in mg/dL

24 h = 1440 min

Expected Creatinine Excretion = 20 mg/kg

70-kg person = 1400 mg total creatinine in 24-hour urine is correct urine collection

24-hour urine volume = 1500 ml or 1.04 ml/min

Urine Creatinine = 93.3 mg/dL

Serum Creatinine = 1 mg/dL

$$Ccl = \frac{93.3 \times 1.04}{1} = 97.1 \text{ ml/min}$$

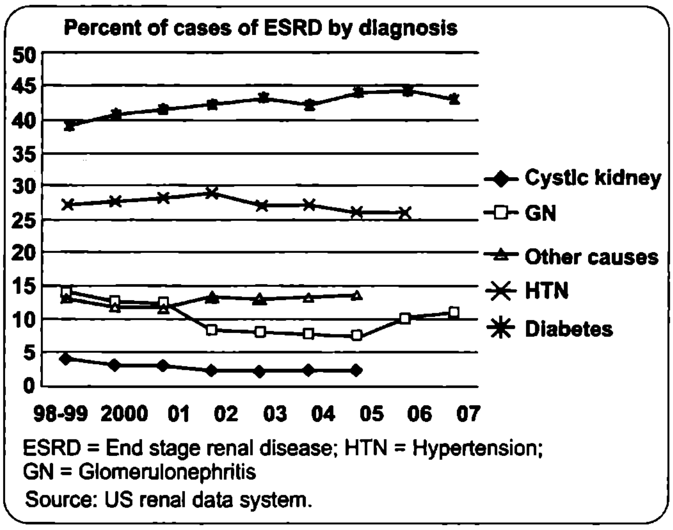
GFR measured by Ccl may not be accurate because of the technique of urine collection which some patients may not be able to follow. Accurate ways to measure GFR are by iothalamate clearance or inulin clearance both of which are cumbersome for office practice. Therefore, we have to settle with Ccl or GFR calculated on the basis of MDRD abbreviated formula which is essentially done from serum creatinine taking into account age, gender and race.

Age (years)	*Average GFR*
20-29	116 ml/min/1.73 m^2
30-39	107 ml/min/1.73 m^2
40-49	99 ml/min/1.73 m^2
50-59	93 ml/min/1.73 m^2
60-69	85 ml/min/1.73 m^2
70+	75 ml/min/1.73 m^2
MDRD Formulae (eGFR)	
Acceptable GFR	=>60 ml/min/1.73 m^2
Chronic Kidney Disease	<60 ml/min/1.73 m^2
Kidney Failure	<15 ml/min/1.73 m^2

Drugs Causing Slowly Progressive Renal Failure or ESRD in the Name of Renoprotection in A Clandestine Fashion

Lisinopril is the commonest (70 percent) of all angiotensin converting enzyme inhibitor (ACEI) drugs to cause ARF and ESRD in elderly patients, patients with uncontrolled diabetes and in those with uncontrolled hypertension. Next to lisinopril is ramipril. To that effect, less offensive ACEI is enalapril and the least harmful is the captopril. Among the angiotension receptor blocking (ARB) group of drugs losartan (Cozaar®) is most commonly associated with ARF or ESRD. Other ARBs including irbesartan (Avapro®), candesartan (Atacand®), telmisartan (Micardis®), olmesartan (Benicar®), or valsartan (Diovan®) are equally offensive to that effect.

These drugs are indiscriminately used to reduce proteinuria and hence reduce the risk of ESRD. Ironically, with excessive use of ACEI and ARB group of drugs, incidence of ESRD in diabetes has increased over the years. More patients with diabetes-related CRF are entering into dialysis programs now than they did 10 years ago as shown in Figure 1. Nephrologists observe in their patients that renal function is deteriorating and when eGFR is less than 20 ml/min, patients are given an advanced warning for preparation of dialysis such as creation of arteriovenous fistula for long-term hemodialysis. Nephrologists intentionally or unintentionally made no attempt to discontinue ACEI, ARB drugs or a combination of both which the patients were receiving, to determine if the renal function improves without the use of these drugs. Therefore, in the opinion of the author, progression of asymptomatic CRF into symptomatic ESRD requiring maintenance hemodialysis or continuous ambulatory peritoneal dialysis is a deliberate act for economic reasons. This will be made crystal clear throughout the chapter by the approach of the author to treat CRF with only one goal in mind which is to make CRF patients live a good life, and not enter into a maintenance dialysis clinic for less than optimal survival.



ESRD = End stage renal disease; HTN = Hypertension; GN = Glomerulonephritis

Source: US renal data system.

Figure 1: End stage renal disease cases by diagnosis

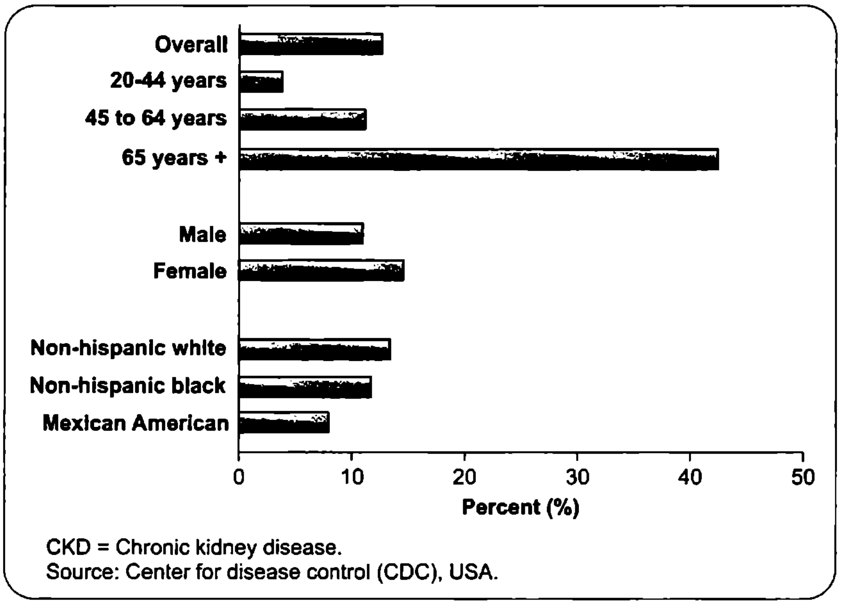
Many more elderly (>65 years) are developing CRF or chronic kidney disease (Fig. 2) and treated in dialysis clinics, thus blaming age, and not the ACEI or ARB drugs that are contributing into ESRD.

There are three possible explanations for elderly people developing CRF and entering into dialysis clinics.

1. Many elderly people have diabetes, hypertension or arteriosclerotic vascular disease which may not be progressive with aging.
2. Many elderly people are evidently taking one or more of the ACEI/ARB drugs for diabetes or hypertension.
3. Most patients with CKD do not progress to ESRD, requiring dialysis, unless they are treated with one or more of the above drugs. Data from the United States ESRD program will be a testimony to the effect that ACEI/ARB groups of drugs have permitted escalation of dialysis programs (Table 1).

Table 1. Data from US ESRD program

YEAR	*ESRD–Dialysis*
1978	14,000
1986	32,000
1993	ACEI entered the market
1994	65,000
1998	75,000
2006	3,54,754
2010	no data available



CKD = Chronic kidney disease.

Source: Center for disease control (CDC), USA.

Figure 2: Chronic kidney disease among US adults

Several patients are presented here to illustrate the paradoxical role of ACEI/ARB in renoprotection and progression to ESRD.

Patient #1—This patient was a middle aged white male who had eight years of follow up in a teaching hospital renal clinic from 1983 to 1991. The average follow up was four times per year. In 1983, he was referred for renal insufficiency with BUN of 29.4 mg/dL and serum creatinine of 1.9 mg/dL. He had no symptoms. His hematocrit was 50.8 percent. His serum calcium, phosphorus and uric acid were all normal.

His average blood pressure was 129/82 mm Hg. He was not on any medicine. One year later, a renal biopsy documented focal glomerular sclerosis. From 1983 till 1988, he remained asymptomatic, showed slight elevation of blood pressure and was not taking any medicine except H_2 blocker. In a period of 5 years, his BUN increased from 29.4 to 43 mg/dL and creatinine from 1.9 to 4.1 mg/dL. During this 5-year period his weight remained essentially unchanged between 182 and 184 lbs. In 1989, for the first time, he became symptomatic of shoulder pain and since then began to develop new symptoms. He gained 10 lbs. weight in 1 year. In 1989, he was placed on lisinopril by a military hospital nephrologist. He continued to gain weight. His BUN and serum creatinine increased to 67 and 5.3 mg/dL, respectively. He became hyperkalemic. Serum potassium was 5.8 mEq/L. CO_2 decreased from 27 to 22 mEq/L and his hematocrit decreased to 35 percent. Nothing was known at that time that ACE inhibitor, lisinopril might be the culprit until an investigation was begun one year later and the data were published in 1994. In 2 years, his BUN and serum creatinine increased two and half time from those in 1988 to 73 mg and 9.8 mg/dL, respectively, in 1991. He required Kayexalate® in sorbitol to control hyperkalemia. His serum phosphorus increased to 8.5 mg/dL and his hematocrit decreased to 34 percent (Table 2). On November 4, 1991 he had a 24-hour Ccl of 16.4 ml/min and a proteinuria of 6.1 g. He was placed on maintenance hemodialysis.

Table 2. Patient #1—serial serum chemistry profile (Quarterly)

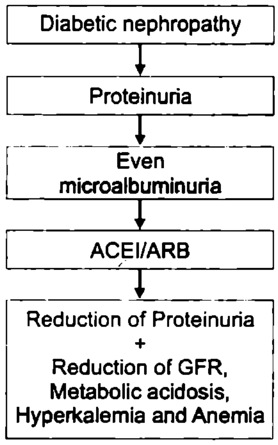
Year	*BUN (mg/dL)*	*SCr (mg/dL)*	*Na (mmol/L)*	*K (mmol/L)*	*CO_2 (mmol/L)*	*UA (mg/dL)*	*HCt (%)*
1983	29	**1.9**	NA	NA	NA	62	51
1984	27	**2.2**	138	4.2	NA	NA	NA
1986	37	**3.2**	141	5.2	27	NA	40
1987	43	**4.1**	145	4.6	25	6.6	41
1989	67	**5.3**	143	5.8	22	8.4	35
1	55	**5.7**	143	5.6	21	7.3	NA
2	48	**5.3**	147	5.0	23	NA	NA
3	57	**5.0**	146	6.1	24	NA	34.6
4	56	**4.9**	147	5.1	24	7.3	NA
1990				Lisinopril started			
1	60	**5.3**	142	5.4	25.0	7.5	37.6
2	58	**5.9**	143	5.1	17.0	7.7	34.6
3	59	**5.8**	143	6.5	22	NA	36.6
4	50	**5.8**	143	4.5	NA	NA	NA
1991							
1	73	**9.8**	143	3.9	27	8.5	34.3
2	68	**8.3**	144	4.3	27	NA	NA
3	73	**9.8**	143	3.9	27	8.5	34.5

SCr = Serum Creatinine, UA = Uric Acid, HCt = Hematocrit, NA = Not Available.

Table 2 will illustrate that with initiation of lisinopril, an ACE inhibitor, his serum creatinine rapidly increased. Concomitantly, his serum potassium increased requiring regular use of Kayexalate® to keep serum potassium under control. Therefore, it is reasonable to state that ACEI, lisinopril hastened the progression of CRF into ESRD requiring dialysis therapy.

Patient #2—81-year-old white female was admitted to a local hospital on August 08, 2006 with a diagnosis of acute renal failure. She gave history of diarrhea three months prior to hospital admission. Medication at the time of hospital admission consisted of metoprolol 60 mg po daily, Plavix® 75 mg po daily and Valsartan (Diovan®) 120 mg po daily. She had already received hemodialysis x one treatment and hence she expressed concern if she had to remain on dialysis treatment. She was seen by the author on August 12 when Diovan® was discontinued and she was started with bicarbonate infusion at 60 ml/hour x 48 hours. She was also prescribed erythropoietic stimulating agent (Epogen®) 10,000 units subcutaneously every 48 hour. She was followed by the author up to August 16 when reversal of ARF and hyperkalemia and increase in hemoglobin were noted (Table 3).

Patient #3—59-year-old white female was admitted in a local hospital on October 1, 2006 with diagnoses of uncontrolled hypertension, diabetes mellitus and advanced CRF. Her home medicines consisted of glyburide, lisinopril, proton pump inhibitor and amlodipine. The dosages of the medicines were not known. On June 25, 2005, she had a 24-hour proteinuria of 5010 mg. She was prescribed lisinopril to reduce proteinuria. On September 30, 2005 her BUN and serum creatinine (SCr) were 45 mg/dL, 4.1 mg/dL, respectively. On October 2, her 24-hour proteinuria was 3071 mg. This reduction of proteinuria was possible at the expense of increase of BUN and SCr to 61 mg/dL and 5.7 mg/dL, respectively. Her SCr increased by 39 percent from September 30 to October 2 (in a period of three days). Author during on-call service discontinued lisinopril and started on bicarbonate infusion. However, her regular nephrologist started her with hemodialysis treatment. This is exactly what is happening in nephrology practice as shown in schematic diagram.


Diabetic nephropathy
Proteinuria
Even microalbuminuria
ACEI/ARB
Reduction of Proteinuria + Reduction of GFR, Metabolic acidosis, Hyperkalemia and Anemia

No interest among the nephrologists to determine if reduction of proteinuria is secondary to reduction of GFR and if discontinuation of ACEI. ARB will restore GFR and reduce BUN and SCr levels.

Table 3. 81-year-old white female

August 2006	*BUN (mg/dL)*	*Cr (mg/dL)*	*eGFR (ml/min)*	*NA (mmol/L)*	*K (mmol/L)*	*CO_2 (mmol/L)*	*Hb (g/dL)*
08	58	2.3	21.6	132	5.7	23	7.8
09	57	2.2	23	134	5.6	24	NA
11	49	2.1	24	134	5.0	30	NA
12	53	2.5	20	138	5.7	30	8.6
Hemodialysis Done x 1. Diovan® discontinued, bicarbonate infusion and Epogen® started							
13	60	3.1	15	135	5.8	29	9.3
Florinef (9, alpha fluorohydrocortisone) for hyperkalemia started							
14	52	2.4	21	140	5.0	31	8.1
15	41	2	25	138	5.1	29	9.3
16	27	1.5	35	138	4.3	27	10.2

She was not author's patient but she was treated by the author during on-call periods.
NA = not available.

Proteinuria in and of itself is benign and has minimal effect on overall renal function. Details will be found in the chapter on Proteinuria on Renal Function.

Why is so much dialysis therapy? According to the author it is a rich men's bargain for banks

Dialysis is a big profitmaking practice for nephrologists and big corporations.

A report from Nephrology News and Issue June 2010 exemplifies author's statement.

The investment company Raymond James estimated the worth of the recent acquisition of American Renal Holdings by Centerbridge Partners LP, a private equity firm, to be worth ***$450 million or about $78,261 per patient****. Raymond James estimated that American Renal Association (ARA) was generating* ***$275 million in annual revenues****. ARA and its physician partners own and operate 83 dialysis clinics treating* ***more than 5,705 patients*** *across the United States.*

Even more dramatic than the above is the increase of freestanding and for profit dialysis clinics (Table 4).

DIABETES-DIALYSIS BUSINESS ENTERPRISE

Here is data from the state of North Carolina (NC) — population 9,222,414.

- The number of patients who visited a dialysis center has increased by 78 percent from 1996 to 2006.
- The increasing incidence of kidney failure means more communities are getting their own dialysis center.
- At the end of 2008, NC had 160 dialysis clinics with 3,841 dialysis machines.

NC has approved an additional 145 dialysis machines, another 128 machines have been requested. WHY?

1. No attention to glycemic control.
2. Over-enthusiastic use of ACEI/ARB

Dreadful Statistics of Hemodialysis Therapy

- US Renal Data System 2006
    - Death: 32,040 diabetic patients on maintenance hemodialysis
    - Annual death rate 23.4 percent
- Austria - 3-year survival
    - Nondiabetic 20 percent
    - Diabetic 17 percent
- 3-year survival equally low in Italy and Brazil

Despite dreadful statistics, why are nephrologists so enthusiastic to recommend dialysis treatment to patients with diabetes-related CRF? There is only one thing to say about that. There is more money in dialysis care than office care.

On the contrary, author treats the patients with CRF of variable severity in the office to render them a symptom-free life which makes them happy and encourage them to return to the office again and again (Table 5).

Although ACEI/ARB has become an armamentarium in diabetes care with progression to ESRD and dialysis therapy, there are instances of uncontrolled diabetes associated with uncontrolled hypertension (stage 3 or 4 hypertension) and rapid progression to symptomatic ESRD requiring maintenance dialysis therapy without the use of ACEI/ARB drugs. Here is one such example. A 41-year-old African-American female was admitted into a local hospital on April 27, 2008 with tingling and numbness of the left side of the face and weakness of

Table 4. Free-standing dialysis units

Parameter	*1995*	*2000*	*2005*	*1995-2000*	*1995-2005*
	Total Number			*Annual %age Change*	
Dialysis facilities	2,721	3,805	4,540	7	5
Hemodialysis stations	40,578	59,480	78,870	8	7
		Percentage of All Facilities			
Hospital-based	26	18	14	0	–1
Free-standing	74	82	86	9	7
For Profit	65	78	78	11	7
Nonprofit	35	22	22	–3	0

Adapted from Himmelfarb J, et al. J Am Soc Nephrol 2007;18:2021-7.

both left sided upper and lower extremities. She gave a long history of diabetes and hypertension. Her blood pressures were sitting 160/120 mmHg and standing 150/110 mmHg. In the hospital, she received lantus insulin 10 units after breakfast and after dinner, labetalol 100 mg po tid, clonidine 0.1 mg tid, amlodipine 10 mg po daily and Neurontin* 100 mg po daily.

Admission Laboratory: Glucose 110 mg/dL (6.1 mmol/L), BUN 30 mg/dL (1.6 mmol/L), SCr 4.3 mg/dL (0.2 mmol/L), eGFR 12.6 ml/min. 24-hour proteinuria April 2008 8.5 g, June 2008 13 g. Thus she had predominantly uncontrolled hypertension with stroke, and nephrotic syndrome. She progressed to develop ESRD. Her glucose control was normal. Questions were asked, if nephrotic syndrome and ESRD were due to mainly uncontrolled hypertension or hypertension and diabetes. A percutaneous kidney biopsy was done to answer those questions.

Histopathology of kidney biopsy revealed widespread glomerular sclerosis, profound tubulointerstitial changes and severe arteriolar sclerosis and hyalinosis (Figs 3 and 4). Whether glomerular sclerosis and tubulointerstitial changes were due to diabetes could not be ascertained. Renal pathologist's general impression was that the changes were consistent with severe or malignant hypertension. Her blood pressure control became difficult and renal function showed no sign of improvement. To achieve BP control and prevent further stroke, she was placed on maintenance hemodialysis x three per, week. As of September 27, 2010, she is doing fine with maintenance dialysis. Her BP is under good control.

Preservation of Nephron Function in Diseased Kidneys

CRF is a progressive disorder. However, the progression may be slow or fast depending on the etiology and concomitant disorders, therapy and procedures. Therefore, close attention must be paid to the remediable factors which may otherwise accelerate the progression

Table 5. Poor man's adventure helping patients stay off dialysis: conservative treatment of advanced chronic renal failure equivalent to CKD Stage 4-ESRD*

*Patient**	*History*	*Initial SCr/eGFR (mg/dL/ml/min)*	*Latest SCr/eGFR (mg/dL/ml/min)*	*Symptoms*	*Activity*	*K (mmol/L)*	*Hb (g/dL)*
1. LM - 76AAF	Hypertension	Jun 2007 3.13 / 15	Apr 2010 4.96/9	None	Full-time nursing assistant	4.1	10**
2. MS - 82WF	Unknown	Oct 2007 4.3 / 10	May 2010 5.01/9	None	Fishing in river	3.8	12.9
3. KP - 70WM	Hypertension	Mar 2008 2.66 / 25	May 2010 2.16/30	None	Active	4.7	13.0
4. CM - 38AAF	Renal transplant rejection	May 2007 2.3 / 29.3	May 2010 2.9/20.2	None	Active	4.8	13.9
5. GB - 70WM	Single kidney, diabetes, recurrent urinary retention	Nov 2004 1.6	May 2010 2.10/33	None	Active	4.1	11.6
6. MB - 54AAF	Hypertension, stroke	Jan 2005 1.6 / 40	May 2010 1.78/38.3	None	Active	3.8	13.1
7. GG - 86AAF	Recurrent hyperparathyroidism	Jan 2005 2.3 / 26.1	May 2010 2.03/25	None	Hip fracture, wheelchair	4.5	11.3**
8. BD - 51AAF	Renal transplant rejection, hypertension	Oct 2006 3.1 / 28	Jan 2010 2.72/23.6	None	Active	3.7	11.7**

CKD = chronic kidney disease; ESRD = end stage renal disease; SCr = serum creatinine; eGFR = estimated glomerular filtration rate; K = potassium; Hb = hemoglobin; AAF = African-American female; WF = white female; WM = white male; AAM = African-American male.

* Few of many patients listed.

** Epogen or Procrit 20,000 units subcutaneously weekly or biweekly.

leading to ESRD and development of symptoms and signs warranting dialysis therapy. The remediable factors are listed in Table 6.

Among all the factors, prescription of ACEI drug such as lisinopril or ARB drug Diovan* or micardis in the name of renoprotection is a very common and disguisable cause of rapidly deteriorating renal function making the patients to seek emergency care. Use of aminoglycosides such as gentamicin, tobramycin or kanamycin in a patient with indolent diabetes-related renal disease will throw the patient into severe and symptomatic renal failure requiring immediate dialysis treatment for symptomatic relief. Cardiac catheterization with coronary angiogram is a common procedure for investigation of chest pain or congestive heart failure in patients with CRF. Although, precautions are taken to minimize the adverse effect of contrast materials on the diseased kidneys, some amount of functional deterioration is still imminent. However, rarely a patient becomes symptomatic warranting dialysis therapy. Renal function deteriorates at a faster rate in a state of consistent postprandial hyperglycemia with glucose levels above 200 mg/dL (>11.1 mmol/L) than when postprandial glucose levels are kept below 200 mg/dL (<11.1 mmol/L).

Table 6. Remediable factors aggravating renal failure

1.	Nephrotoxic Drugs or Agents: ACE1/ARB, NSAID, Aminoglycosides, Radio-contrast Materials
2.	Diuretic therapy
3.	Uncontrolled diabetes
4.	Fluid Loss from other causes, such as vomiting, diarrhea
5.	Uncontrolled hypertension
6.	Recurrent urinary tract infection
7.	Unilateral or bilateral urinary tract obstruction
8.	Hypokalemia
9.	Hyperuricemia
10.	Hypercalcemia

High dose diuretic therapy such as intravenous furosemide 40 mg intravenously twice daily typically prescribed for congestive heart failure in a patient with CRF can rapidly deteriorate renal function. Even high dose oral furosemide and metolazone will lead to ARF on the top of CRF. Diuretic-induced ARF rarely gives rise to symptoms and signs requiring dialysis therapy. Diuretic-induced ARF is almost always reversible with discontinuation of diuretics or reduction of the dose of diuretics and intravenous fluid therapy. Hypokalemia and hyperuricemia are serious adverse effects of diuretic therapy as shown in Table 7. Hyperuricemia is often an obscure cause of ARF in a patient with indolent CRF. Rapid excretion of uric acid by bicarbonate infusion and inhibition of uric acid biosynthesis with allopurinol often reverses ARF.

From Table 7, it should be noted that 11 pounds weight loss accompanied by sensible increases in hemoglobin and hematocrit, BUN and CO_2 indicate profound decrease in effective arterial blood volume (EABV). The latter is the main cause of marked increase in serum

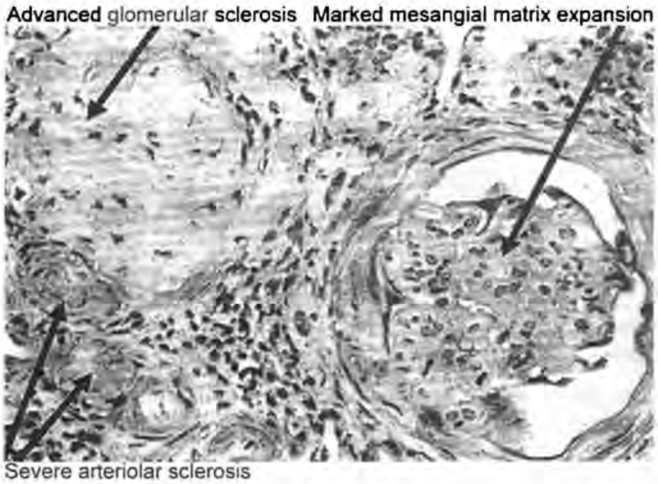

Advanced glomerular sclerosis
Marked mesangial matrix expansion
Severe arteriolar sclerosis

Figure 3: Trichrome stain

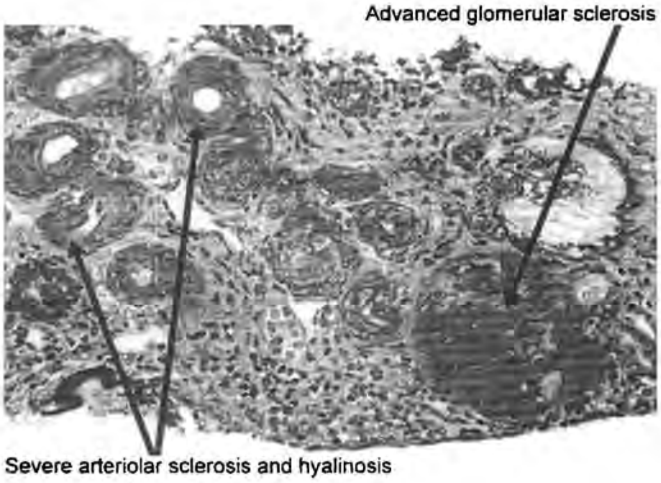

Advanced glomerular sclerosis
Severe arteriolar sclerosis and hyalinosis

Figure 4: Periodic acid Schiff stain

uric acid from 8.4 to 13.2 mg/dL. Hypercholesterolemia as seen on August 23 is secondary to EABV deficiency and requires no antilipidemic therapy. Similarly, hyperglycemia is common secondary to EABV deficiency although not seen in this patient but seen in the next patient (Table 8).

Hyperglycemia mimicking established diabetes (> 200 mg/dL or 11.1 mmol/L) is common with hydrochlorothiazide (HCTZ) prescriptions for hypertension. This HCTZ-induced hyperglycemia is frequently interpreted as Type 2 diabetes and results in prescriptions of oral antidiabetic agents. The previous patient (Table 7) associated with EABV deficiency from high dose of furosemide did not develop hyperglycemia but this patient did suggesting that HCTZ per se may be diabetogenic.

Table 7. RH 74-year-old white male diagnosis: congestive heart failure

1993	*May 12*	*August 23*
Therapy	Furosemide 40 mg po bid	Furosemide 60 mg po bid + metolazone 2.5 mg. po once daily
Weight (lbs)	**191**	**180**
BP mmHg (sitting)	122/63	129/76
Hemoglobin (g/dl)	**11.9**	**14.5**
Hematocrit (%)	36.3	43.5
BUN (mg/dL)	**37**	**67**
Serum creatinine (mg/dL)	**1.6**	**1.8**
Serum Na (mmol/L)	139	141
Serum K (mmol/L)	**4**	**3**
Serum chloride (mmol/L)	**104**	**88**
Serum CO_2 (mmol/L)	**29**	**39**
Serum glucose (mg/dL)	92	89
Serum uric acid (mg/dL)	8.4	13.2
Serum cholesterol (mg/dL)	151	200

NONDIALYSIS TREATMENT OF CRF

Goal of this treatment is preservation of intact nephron function-intact nephron hypothesis (Sir Robert Platt).

The key word for a CRF patient is a vigilant care, which encompasses adequate control of fluid, electrolytes and blood pressure, detection and treatment of urinary infection, no use of nephrotoxic drugs and avoidance of the use of agents that are potentially nephrotoxic. A best example of the latter is radiologic study with a contrast in those with impaired renal function.

Maintenance of extracellular fluid volume including blood volume; blood pressure, blood glucose and potassium balance are critically important in the preservation of renal function. Rapid loss of fluid as a result of vomiting, diarrhea, high fever, working in hot humid weather associated with excessive perspiration will rapidly decrease renal function in a patient with CRF. ***Here is a prime example.***

CD, a 68-year-old white male is a regularly scheduled patient in the author's office. He developed ARF requiring temporary hemodialysis, but he recovered resulting in discontinuation of hemodialysis. He stabilized at a renal function of low 2 mg/dL SCr and eGFR of 33 to 35 ml/min. He remains asymptomatic and is followed in the office every five to six weeks. At a office visit of August 6, 2010, his renal function was noted to be lower than expected. Author discussed with him for the possible cause of rapid deterioration of renal function. It was learnt that he works in his garage for long hours fixing his antique car. At that time outside day time temperature was ranging from 95 to 97°F. Inside the garage it could be 105°F and hence losing body fluid excessively and out of proportion to replacement. To assess the body fluid status, he was

Table 8. HW 71-year-old white male

Year 1995	*Glucose (mg/dL)*	*BUN (mg/dL)*	*Cr (mg/dL)*	*Na (mmol/L)*	*K (mmol/L)*	*Cl (mmol/L)*	*CO_2 (mmol/L)*
June 14	234	55	4.4	138	3.4	93	27
Hydrochlorothiazide discontinued June 14							
July 11	92	33	3.4	144	4.1	109	18
Cr = Serum Creatinine.							

sent to the laboratory for the urine to be analyzed for electrolytes and creatinine. Author advised him to drink 1.5 liters (45 ounces) of additional fluid, while he was working in the garage and repeat his lab work in 2 weeks. The results are shown in Table 9.

Analysis of urinary findings of July 29: Low urinary Na with more than twice urinary K indicates volume depletion (Normal UNa 60, UK 40) This is strongly supported by very high urinary creatinine level (Normal = 100 mg/dL). Such urinary creatinine indicates very concentrated urine. Additional intake of fluid resulted in repletion of body water, improvement in renal function as well as increase in urinary Na and decrease in urinary creatinine. Similarly, hemorrhage, especially visceral hemorrhage, even of small amount, can rapidly decrease renal function. Therefore, replacement of blood, promptly and adequately, will restore renal function to a great extent, whereas, delay could result in acute tubular necrosis with irreversible renal failure.

Marked and rapid reduction of blood pressure (BP) with systolic BP to less than 100 mmHg as a result of fluid or blood loss or too many antihypertensive drugs will similarly reduce renal function at a rapid rate. It is important to adjust antihypertensive therapy downward in a patient with fluid or blood loss and on the basis of upright BP. Persistent glucosuria in uncontrolled hyperglycemia can impair renal function, whereas, tight glucose control with insulin therapy will reduce the burden of filtered glucose load into tubules and prevent tubulointerstitial damage and impairment of renal function. Hypokalemia can cause swelling of the tubular epithelial cells and diminish renal function. Finally, diuretic therapy is a common practice in patients with CRF to control fluid and salt balance and blood pressure and to minimize swelling. Although diuretic therapy has a proven benefit in controlling fluid and electrolyte balance in CRF, overuse of diuretics could cause further deterioration of renal function and offset the benefit.

Prevention and Nondialytic Treatment of CRF

A patient with CRF is typically an office or clinic patient. Such a patient seldom requires hospital admission unless fluid overload leads to congestive heart failure; develops gastrointestinal symptoms or chest pain.

A frequent office visit as illustrated in Tables 2 and 5, to check weight, blood pressure, any symptoms, hemoglobin, hematocrit, BUN, SCr, potassium, carbon dioxide, calcium, phosphorus and uric acid is essential to reduce the risk of rapid progression of CRF. Periodically, parathyroid hormone (intact PTH) is necessary to obtain to determine parathyroid activity which has a severe impact on osseous structure. These patients may be cared for by internal medicine physicians, other than nephrologists. In general, close attention is to be given to their medicine list, which may be a source of rapid progression of CRF to ESRD and development of symptoms.

Diet: Evidence is fairly convincing that a low protein but high calorie diets prevent progression of CRF. Groups were compared between normal protein intake (0.8 to 1 g/kg) and low protein intake (0.4 g/kg). A significantly greater percentage of patients taking a normal amount of protein progressed to ESRD at a faster rate than the group taking a low protein diet. Also, gastrointestinal symptoms, such as nausea, vomiting, loss of appetite, are more common among those with normal protein intake, than in those with low protein intake. In another study, two groups of patients with average Ccl of 31.5 ml/min and 34.7 ml/min, average 24-hour proteinuria of 1.6 g and 1.8 g and with normal blood pressure were treated with either conventional protein diet or low protein diet. They were followed for a period of 60 months.

Table 9. CD 68-year-old white male

Date 2010	*BUN (mg/dL)*	*Scr (mg/dL)*	*eGFR (ml/min)*	*Hb (g/dlL)*	*UNa (mmol/L)*	*UK (mmol/L)*	*UCr (mg/dL)*
June 29	22	2.07	34	12.8	ND	ND	ND
July 29	39	2.48	28	14.2	27	59	335.4
Recommended additional 45 ounces of fluid per day while working in hot garage. He followed the advice.							
August 24	31	2.13	33	12.9	103	14	75.5
ND = not done.							

SCr: Serum creatinine, VCr: Urinary creatinine

The survival to end point (death) was significantly lower in the group treated with conventional protein diet compared to the group treated with low protein diet.

It has been shown that dysmotility-like dyspeptic complaints and delayed gastric emptying are prevalent in CRF patients whether they are diabetic or not. Gastrointestinal manifestations consisting of nausea, vomiting, loss of appetite and diarrhea are common in CRF especially with rising BUN. Rising BUN can be mostly due to unrestricted protein intake. Therefore, mild to moderate restrictions of protein intake (50 to 60 g/day) is essential to minimize the rise of BUN and keep down the development of gastrointestinal symptoms. Protein intake should be further restricted (40 g/day) with declining renal function (Ccl equal or less than 25 ml/min). Protein restricted diet is disadvantageous because of malnutrition which affects survival, but it has some advantages. These are: 1) a low-protein diet minimizes metabolic acidosis, hyperkalemia, hyperphosphatemia and hypertension by reducing intake of sulfate, phosphate, potassium and sodium, 2) a low-protein diet can slow down the progressive loss of renal function in some patients, and 3) a low-protein diet reduces the severity of uremic symptoms.

On the other hand, low protein diet has distinct disadvantages 1) low intake of essential amino acids lead to negative nitrogen balance and hypoalbuminemia, 2) Proteinuria further adds to hypoalbuminemia.

Hypoalbuminemia in, and, of itself, is an independent risk factor in uremic patients without or with dialysis. However, if liver and pancreatic function are unaffected, malnutrition is generally less severe.

Beneficial role of vitamins except vitamin D, and minerals except calcium in undialyzed patients is undocumented.

Specific Treatment

Hypertension

Blood pressure is variably elevated in patients with CRF. Blood pressure elevation could be multifactorial. However, volume overload is common which is easily detected by rapid weight gain. Blood pressure control (≤ 140/80 to 120 to 130/70 mmHg) is essential to preserve nephron anatomy and function. Avoid lowering BP to very low level (< 120/70 mmHg) which will readily reduce renal blood flow in failing kidneys.

A combination of beta blocker (atenolol or metoprolol 50 mg daily) and second generation dihydropyridine calcium channel blocker, such as amlodipine or isradipine 5 to 10 mg once or twice daily is very effective in reducing BP. Other safe antihypertensive drugs include methyldopa (Aldomet®) 250 to 500 mg po tid or labetalol 100 to 200 mg tid, Clonidine 0.1 mg to 0.2 mg po tid Avoid use of Aldomet® or clonidine in active individuals because of drowsiness and falling asleep during driving. In resistant cases (suspect volume overload), hydrochlorothiazide or chlorthalidone 12.5 to 25 mg po daily is recommended. In resistant hypertension despite three to four lines of antihypertensive therapy, possibility of unilateral or bilateral renal artery stenosis is a consideration. However, investigations to elucidate that possibility such as MRA, contrast renal arteriogram is associated with serious risk on the surviving nephrons. Therefore unpredictable benefits from the radiological procedures must be carefully weighed against the serious hazards, before decision is made to go ahead with the procedures. Captopril renal scintigraphy is a sensitive test and reasonably safe but would be difficult to interpret in patients with CRF. Author's recommendation is to obtain plasma renin activity and aldosterone levels and based on these results determine what should be done next.

In very resistant hypertension minoxidil 5 to 10 mg po in combination with furosemide 40 mg po daily can be effective in lowering BP. Alert patients to excessive hair growth, which may be nuisance for the female patients. Adjuvant therapy, such as potassium chloride 20 to 40 mEq po daily may be necessary associated with diuretic therapy. Pericardial effusion has been reported with use of minoxidil.

Hyperkalemia and Metabolic Acidosis

Both are uncommon or mild in steady state CRF. Both are common and often can be severe with use of—

1. ACEI/ARB group of drugs
2. Nonsteroidal anti-inflammatory drugs
3. High protein meals
4. Eating too many fruits

Hyperkalemia and metabolic acidosis are consistent features in those associated with hyporeninemia and hypoaldosteronism. Hyporeninemia and hypoaldosteronism are common in chronic renal disease where tubulointerstitial changes are severe which include, diabetic nephropathy, sickle cell disease, toxic nephropathy or unknown chronic tubulointerstitial nephritis. Aldosterone promotes potassium and hydrogen ion secretion, thus hypoaldosteronism results in hyperkalemia and metabolic acidosis. Sodium and volume overload will further reduce aldosterone production and could aggravate hyperkalemia and metabolic acidosis. Management plan consists of:

1. Obtain urinary electrolytes to determine urinary sodium and potassium excretion
2. Obtain plasma renin activity and plasma aldosterone levels, and
3. An arterial blood gas to document metabolic acidosis.

A very effective treatment of hyperkalemia and metabolic acidosis associated with hypoaldosteronism is 9-L-fluorohydrocortisone (Florinef®). It is an aldosterone analog. The starting dose is 0.1 mg orally once a day. 0.1 to 0.2 mg once daily is generally adequate to maintain normokalemia and near normal bicarbonate level. Florinef causes sodium and water retention and therefore, should be used cautiously in those with a history of hypertension and congestive heart failure (CHF). Other treatment modalities include: 1) liberalization of salt intake to promote potassium and hydrogen ion exchange but again this therapy is fraught with the risk of sodium-volume overload and precipitation of CHF. 2) Kayexalate®. This is a time honored and very effective therapy to control hyperkalemia. Kayexalate® must be dispensed in 30 percent sorbitol and prescribed as Kayexalate® in sorbitol 5 g in 20 ml. Depending on the level of initial serum potassium level, usual prescription is 20 ml every 6 to 8 hours until serum potassium decreases to a safe level of less than 5.5 mEq/L. The maintenance dose is 20 ml twice daily. Sorbitol may result in loose bowel movement, not necessarily frank diarrhea, but it promotes more potassium excretion through the bowel. Kayexalate® mixed with water should be prescribed for those with diabetes as sorbitol may markedly increase glucose level in diabetes. The worst drawback of Kayexalate® is its ugly appearance and bad taste, which are not welcomed by most patients.

Deposit of Kayexalate® crystals in the gastrointestinal tract associated with ulceration has been reported. Nevertheless, cation exchange resin is beneficial not just to control hyperkalemia but its use has been noted to improve renal function. Here is an example. A 69-year-old African-American female has chronic kidney disease stage 3 due to hypertension and diabetic nephropathy. In a office visit on June 2, 2010 she was found to be mildly hyperkalemic. Author prescribed her Kayexalate® 5 g po mixed with water daily x 5 days and advised to repeat basic metabolic panel in 10 days. The results are shown in Table 10.

Please note that reduction in serum K was associated with marked reduction in BUN, SCr and increase in eGFR.

Metabolic Acidosis

Adverse Effects

Hydrogen ion readily diffuses into the cells and can retain sodium and water. Thus metabolic acidosis may give rise to pulmonary edema with increased shortness of breath, and cerebral edema with confusion, disorientation, coma and convulsion. Metabolic acidosis stimulates irreversible degradation of the essential branched-chain amino acids and degradation of protein in muscle. It also suppresses albumin synthesis. Protein degradation in the forearm muscle is higher with lower serum bicarbonate. Finally, a significant relationship is found between metabolic acidosis and mortality. Therefore, it is imperative to treat metabolic acidosis to reduce the risk of the onset of congestive heart failure and altered mental state and the risk of mortality.

Diagnosis and Treatment

In the chemistry panel carbon dioxide (CO_2) represents bicarbonate. Thus, low CO_2 indicates low bicarbonate. Low bicarbonate can be found in metabolic acidosis or respiratory alkalosis. An arterial blood gas analysis is essential to distinguish between these two acid-base disorders. pH will determine if low bicarbonate is associated with acidemia ($pH<7.4$) which is metabolic acidosis or alkalemia ($pH>7.4$), which is respiratory alkalosis. Carbon dioxide tension (PCO_2) will determine whether compensation is appropriate or inappropriate. PCO_2 will decrease by 1 to 1.5 mmHg for each mEq decrease in bicarbonate. Higher or lower decrease in PCO_2 means mixed disorder.

Table 10. BN 69-year-old African-American female

2010	*June 2*	*June 11*
BUN (mg/dL)	62	39
SCr (mg/dL)	1.86	1.46
eGFR (ml/min)	28	37
K (mmol/L)	5.2	4.1

Metabolic acidosis is treated by sodium bicarbonate 650-mg tablet, 1 to 2 tablets 2 to 3 times daily, depending on serum CO_2 level. Bicarbonate may cause gaseous distension of the abdomen or belching which makes a patient feeling uncomfortable. An alternative preparation is Bicitra® (Shohl's solution), a mixture of sodium citrate and citric acid. Sodium citrate is converted into sodium bicarbonate endogenously. This liquid preparation is better tolerated than sodium bicarbonate tablet by most patients but is not effective as sodium bicarbonate. The usual dose is 10 to 20 ml 3 times daily. It is important to keep CO_2 in the chemistry panel close to 24 mmol/L. If CO_2 decreases below 20 mmol/L, increase sodium bicarbonate 650 mg x 2/4 times daily. Sodium retention with increase of extracellular volume and slight increase of BP may be noted. If those happen, prescribe furosemide 40 mg po daily or bumetanide 1 mg po daily to reduce volume overload.

Hypertension, Sodium, and Volume Homeostasis

Hypertension may be the cause or effect of renal disease. Uncontrolled severe hypertension will almost invariably lead to renal failure or uremia. While this is less common nowadays because of public awareness of the danger of high blood pressure and availability of effective therapy, association of hypertension with renal disease is still quite common. Dietary indiscretion, lack of regular exercise, stress of daily life, smoking, and use of birth control pills among the women further accentuate the problem. Irrespective of the cause and effect relationship, uncontrolled hypertension is highly conducive to deterioration of renal function. Therefore, keeping blood pressure under adequate control is an important step in the preservation of renal function. There is much controversy about the adequacy of blood pressure control. In the author's experience, adequate control is systolic 130 to 140 mm Hg and diastolic 70 to 80 mmHg, which gives a mean arterial pressure (MAP) of 93 to 96 mm Hg. MAP can be calculated as follows:

$$\frac{\text{Systolic} + 2\ \text{diastolic}}{3}$$

Some authors recommend MAP of less than 90 mm Hg.

Lowering of MAP to less than 90 mm Hg may pose a serious risk of postural hypotension, dizziness and fall. Upright blood pressure recording must be done and antihypertensive therapy must be adjusted accordingly, to prevent postural hypotension and fall.

When renal function is decreased, caution must be exercised in the choice of antihypertensive therapy. Most of the antihypertensive class of drugs is safe to treat hypertension. ACE inhibitor or ARB may not be used at all, due to their adverse effect on renal function and because of increased propensity to cause hyperkalemia. As renal function continues to deteriorate, fluid and salt retention accompanied by a rise in blood pressure becomes a common feature. A diuretic such as loop diuretic, furosemide 40 mg orally twice daily or bumetanide 1 mg orally twice daily is generally adequate to control salt and water retention and as an adjuvant to antihypertensive therapy. Fluid and salt retention can be intractable in renal disease associated with heavy proteinuria and hypoalbuminemia, and will warrant additional diuretic to block distal reabsorption of sodium and water. To achieve that goal, a combination of loop diuretic and hydrochlorothiazide 25 mg once or twice daily or metolazone 2.5 to 5 mg once daily is recommended. Diuresis prompted by a loop diuretic or a combination of diuretic is frequently accompanied by elevation of BUN and creatinine. Elevation of BUN and creatinine will be more marked with a concomitant use of ACE inhibitor or ARB. Use of these classes of drugs also will severely attenuate, the response of diuretics and markedly decrease urine output.

In case of generalized edema (anasarca) associated with severe hypoalbuminemia (equal or less than 2 g/dL), albumin infusion of 50 g followed by an intravenous bolus of 40 mg furosemide (Lasix®), 50 mg torsemide (Demadex®) or 1 mg bumetanide (Bumex®) is likely to induce a optimal diuresis. Moderate restriction of fluid and salt intake is additive to diuretic therapy in the control of hypertension, edema or CHF, complicating CRF.

Calcium - Phosphorus Homeostasis

Calcium and phosphorus homeostasis is altered in CRF, giving rise to hypocalcemia and hyperphosphatemia. Hyperphosphatemia is mostly due to retention of phosphorus, whereas, hypocalcemia is in part due to hypoalbuminemia and in part due to diminished formation of 1, 25 $(OH)_2$, vitamin D_3 by the diseased kidneys.

Mild hyperphosphatemia is found more consistently than hypocalcemia, both of which give rise to secondary hyperparathyroidism. Serum phosphorus increases in parallel with the progression of renal failure. However, the pattern is not the same with serum calcium. As serum phosphorus increases, parathyroid hyperactivity and renal osteodystrophy develops. In addition, calcium x phosphorus product increases, which causes calcification of the vascular system. Widespread calcification of the peripheral vessels, coronary and pulmonary vascular system can be observed by radiologic studies in ESRD with uncontrolled hyperphosphatemia.

A most serious detrimental effect of vascular calcification is ischemic cutaneous ulceration. These ischemic ulcers can be widespread, painful and are difficult to ameliorate.

Successful treatment of hyperphosphatemia to lower serum phosphorus to normal or near normal level and maintain that level is a formidable task. Treatment consists of dietary restriction of phosphorus intake and prescription of phosphate binders.

Dietary restriction comprises reduction of intake of dairy products, such as, milk, cheese, and butter, which should be avoided or consumed minimally. Not many patients comply with this type of restricted diet. The most potent phosphate binder is aluminum hydroxide gel. Aluminum hydroxide gel taken orally during each meal potently binds phosphorus and is excreted through the bowel. Serum phosphorus is reduced predictably with aluminum therapy. However, there are two major drawbacks of the use of aluminum hydroxide gel. These are: 1) It is a very constipating agent, which will delay evacuation of the product and permit absorption of aluminum. 2) Dialysis dementia was attributed to elevated serum aluminum level; consequently its use was prohibited. Dementia or altered mental state is very common among hemodialysis patients and a common cause of hospital admission, although, these patients were not treated with aluminum hydroxide gel. Therefore, there is no justifiable reason to incriminate aluminum as the cause for dialysis dementia. Severe constipation is perhaps the more important reason for not using aluminum hydroxide gel. Nevertheless, it works and is especially useful in those with intractable hyperphosphatemia. However, for fear of aluminum toxicity, which is unwarranted, use of this effective agent, has been completely abandoned in the nephrology community, Some nephrologists still use it sparingly when more popular agents have failed to control hyperphosphatemia.

A most common agent is calcium acetate and available as 667-mg tablet. One to three tablets three times daily with meal is commonly prescribed. The preparation is called Phoslo® and expensive. Calcium carbonate in the form of Tums® is also prescribed, well tolerated and inexpensive. A major side effect is hypercalcemia in addition to its ineffectiveness to lower serum phosphorus adequately.

Another preparation is called Renagel® and getting popular due to heavy campaign by the manufacturer that it doesn't increase calcium x phosphorus product, and thereby reduces the risk of coronary calcification. This claim will be difficult to substantiate as dialysis patients have multiple risk factors for high incidence of coronary artery disease. High percentage of pre-dialysis patients are diabetic and hypertensive: two most important factors in endothelial dysfunction, microthrombi formation and vascular occlusion. There is new product called lanthanum carbonate which is getting popular. Hyperphosphatemia is a consistent problem among the dialysis patients. Author has an important question why are all these patients on dialysis? Dialysis has turned into a big business for the corporations, industries and professionals. Author finds no hyperphosphatemia among his office patients with CRF. Therefore, it appears that dialysis in and of itself is responsible for hyperphosphatemia, permitting big business for the industries.

Vascular Catastrophe

Widespread vascular disease, consisting of coronary artery disease and cerebrovascular disorders are common in pre-dialysis patients. The incidence of these vascular diseases increases as renal failure progresses to end stage renal failure.

Anemia

Progressive anemia is a consistent feature of CRF. Anemia is mostly due to lack of erythropoietin. Other causes include malnutrition and minute blood loss through the gut. Anemia increases the fatigability and tiredness in these patients. If they have coronary artery disease, anemia can manifest angina, and increase the propensity to cardiomyopathy and congestive heart failure.

A frequent prescription in these patients is a daily aspirin to prevent vascular catastrophe. This medicine can cause more harm than benefit in a CRF patient by inducing gastritis and ulceration, resulting in slow blood loss and anemia. Therefore, careful thought should be given to prescribe aspirin by balancing benefit vs. harm. In every patient with anemia it is a duty to order stool examination for occult blood and serum ferritin and iron saturation to rule out loss of blood through the gut. It is important to know that not every patient with CRF will develop anemia and will require erythropoietic stimulating agent. This is already shown in Table 5.

Treatment of anemia is replacement of erythropoietin as Epogen® or Procrit®. 4,000 to 6,000 units subcutaneously 3 times a week until the hemoglobin increases to 12 g/dL and hematocrit to 36 percent. Then continue with a maintenance dose of 4,000 to 6,000 units subcutaneously once or twice weekly. Benefit is substantial. Most patients experience increased sense of well being and increased exercise tolerance, more than those with hemoglobin in the range of 8 to 9 g/dL. However, there are many adverse effects of this therapy. The most important one is the expense. It is a very expensive therapy. Unless there is a provision of insurance or government plan, it is most difficult for individuals to pay for this drug. Other adverse effects are hypertension and thrombotic events, neither of which is of any major concern. Overall benefit of this therapy far outweighs clinical adverse effects. The only question is whether this therapy improves renal function and delays the need of dialysis is unknown at this time.

Finally, next patient's profile will reveal to the readers that intensive office follow up of patient with CRF is permissive of a good and healthy living without the aid of dialysis therapy (Table 11).

KEY POINTS

1. Uncontrolled diabetes and uncontrolled hypertension are the two most common causes of CRF.
2. Detection at an early stage and maintenance of adequate glycemic and blood pressure control slow down the progression of CRF.

Table 11. Long-term follow up of patient (MS 74-year-old white female) with CRF: history of acute renal failure; hospitalized–recovery; follow up May 2003–July 2010; lives in assisted living facility; enjoys life. Weight: Aug 2003=181 lbs; Jul 2010=198 lbs.

Month/Year	*Symptom*	*BUN/Cr (mg/dL)*	*eGFR/Ccl (ml/min)*	*K (mmol/L)*	*CO_2 (mmol/L)*	*Hb* (g/dL)*
May 2003	SOB on exertion	15/1.5	NA	4.1	21	13.7
Lasix D/C						
July 2006	As above; weight gain 7 lbs in 3.4 mos	52/3.0	37.5	4.6	26	11.4
Toprol®, Plavix®, Lipitor®						
April 2007	As above; 8 lb gain	32/3.4	21.1	4.5	27	12.1
Lasix® 40 mg Mon-Fri, calcitriol						
Sept 2007	As above	44/4.4	NA	3.9	26	11.9
Calcium 11.8, Calcitriol D/C						
April 2008	As above; 7 lb gain	33/2.8	NA	3.8	25	NA
Dec 2008	As above	39/2.69	NA	3.9	26	12.8
Feb 2009	As above	22/2.46	NA	4.4	25	13.6
Toprol XL®, calcitriol, Plavix®, $FeSO_4$. Prescription: Lasix® 40 mg daily						
Sept 2009	As above	25/2.5	<60	4.1	26	12.4
July 2010	As above	29/2.8	17.5	4.5	28	12.1
Weight gain 17 lbs. in 7 years						

SOB = shortness of breath; NA = not available.

Overall Assessment July 2010

1. Feels shortness of breath during walking from her room to dining room.
2. East 3 meals (unrestricted) a day
3. Watches TV, enjoys life.
4. Feels too sleepy, Mellaril® reduced.

3. Frequent office visits to review the controls are essential.
4. Correction of metabolic acidosis with sodium bicarbonate is the cornerstone of therapy.
    - A recent report shows that bicarbonate supplementation slows the rate of progression of renal failure to ESRD and improves nutritional status of patients with CRF.
5. Control of metabolic acidosis and hyperkalemia delays not only the development of symptoms and the need for dialysis but reduces the morbidity and mortality.
6. Treat hypertension with calcium channel blockers, beta blockers, sympathetic inhibitors or a combination of all of these.
7. Maintenance of fluid volume and prevention and replacement of loss of fluid or blood in a timely fashion is very important to prevent rapid deterioration of renal function.
8. ACEI/ARB and other nephrotoxic drugs should be avoided to preserve the remaining renal function.

SUGGESTED READING

1. de Brito-Ashurst I, Varagunam M, Raftery MJ, and Yaqoob MM. Bicarbonate supplementation slows progression of CKD and improves nutritional status. J Am Soc Nephrol 2009;20:2075-84.

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Effect of Proteinuria on Renal Function in Diabetic and Nondiabetic Renal Disease

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ABSTRACT

The pathophysiology of proteinuria is poorly understood. Only subtle evidence exists regarding adverse effects of proteinuria on renal function. However, the belief that reduction of proteinuria will reduce the risk of end stage renal disease (ESRD) has highly influenced clinicians to treat proteinuria with angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) drug therapy. Our objectives are to examine if proteinuria affects renal function and if ACEI/ARB drug therapy preserves renal function by reviewing literature on proteinuria and examining clinical evidence. Like the older literature, we have found that heavy proteinuria, persisting for years, had no effect on renal function in nondiabetic and diabetic nephropathy in contrast to claims of clinical trials that treatment of proteinuria with ACEI/ARB drugs reduces risk of ESRD. We observed that diabetics and nondiabetics, treated with ACEI/ARB drugs, frequently develop acute renal failure or progression of chronic renal failure into ESRD requiring dialysis therapy. Proteinuria in ACEI/ARB-treated patients is reduced but in parallel with reduction of creatinine clearance (Ccl). A different approach to elucidate pathophysiology of proteinuria and to treat proteinuria accordingly are required. The authors' observations indicate that proteinuria is benign and its severity does not parallel progressive kidney disease. On the other hand, use of ACEI/ARB therapy to reduce proteinuria is accompanied by serious adverse effects and escalating health care costs.

OVERVIEW OF CURRENT STATUS OF TREATMENT OF PROTEINURIA

Proteinuria in diabetic and nondiabetic renal disease is a prevalent issue in current medical practice and is associated with increasing pressure to treat proteinuria, including microalbuminuria, with ACEI, ARB, or a combination of both groups of drugs. The medical literature is filed with publications supporting the use of these drugs. The premise in these publications is that reduction of proteinuria will delay progression of diabetic or nondiabetic nephropathy into ESRD. In diabetes, proteinuria has been attributed to glomerular hyperfiltration and, by reducing glomerular hyperfiltration with ACEI/ARB therapy, proteinuria can be reduced and glomerular sclerosis can be mitigated. Many studies contradict this hypothesis. A recent study found no benefit of treating microalbuminuria or proteinuria with ACEI therapy in diabetes. On the contrary, this study found progression of microalbuminuria to overt proteinuria in those who were treated with ACEI. Poor glycemic control and elevated serum cholesterol were the major predictors for progression of microalbuminuria to overt proteinuria in diabetes while on ACEI treatment. Similarly, a previous study from this group showed that in diabetic patients with microalbuminuria, the risk of progression to overt proteinuria was reduced by improved glycemic control. Other studies are in agreement that adequate glycemic control (2h-postprandial glucose <200 mg/dL; HbA1c <7.5 percent) is fundamental to mitigation of progression of proteinuria and preservation of renal function. We have observed that a decrease in proteinuria with ACEI or ARB therapy is associated with a parallel reduction in renal function, suggesting that a decrease in proteinuria is related to a decrease in overall renal function (Table 1). Other investigators have found that long-term use of ACEI therapy is associated with a high risk of ESRD.

The incidence of diabetes-related ESRD has increased over the years despite the prevalent use of ACEI/ARB therapy that is intended to reduce the rate of ESRD (Fig. 1). In Canada, the number of patients diagnosed with diabetes-related ESRD overall rose 114 percent to more than 2100 cases from just under 1100 cases between 1995 and 2004. The rate of new kidney failure diagnoses among diabetes tripled over the period. Since ACEI/ARB therapy has not been successful in reducing the rate of diabetes-related ESRD, it is obvious that something is missing in achieving this outcome. By examining the huge body of evidence on the salutary effects of glycemic control in diabetes, one can infer that little or no attention to glycemic control is the central missing component of the unaccomplished objectives of the clinical trials in reducing the rate of ESRD.

In this chapter, we examine the dichotomies between the popular belief that treatment of proteinuria with ACEI/ARB is beneficial and the contrasting reports on the increasing incidence of adverse effects associated with this therapy. To that effect, we have asked two important questions: (1) Does proteinuria have an impact on renal function? (2) Can ACEI/ARB therapy, intended to reduce proteinuria, preserve renal function? In order to answer these questions, we have reviewed the older literature on proteinuria, when ACEI/ARB drugs were not available, and patients with diabetic and nondiabetic proteinuria are presented to exemplify that persistent proteinuria is not, but ACEI/ARB therapy is, adverse to renal function.

Review of the Older Literature on Nondiabetic Proteinuria Renal Disease

1. Persistent heavy proteinuria or nephrotic syndrome in membranous glomerulonephritis is a classic example to critically examine the important issue as to whether proteinuria should be treated. In that regard, a report on 100 consecutive patients with biopsy-proved membranous nephropathy is considered. These patients received a diuretic or antihypertensive drug as needed but received no glucocorticoids or immunosuppressive drugs. Their urinary protein excretion and serum creatinine concentrations were measured every 6 months for a mean period of 52 months. The baseline proteinuria in 100 patients ranged from 0.2 g to >10 g per 24 h with a mean of 5.1 ± 3.6 g per 24 h. The baseline mean serum creatinine was 1.1 ± 0.5 mg/dL and the mean Ccl was 95.5 ± 36.1 ml/min/1.73 m^2. During follow up, ESRD requiring regular dialysis developed in 14 patients after a mean interval of 71 ± 32 months. Among the remaining 86 patients at the last visit, 68 had renal function that

Table 1. Serially 24h proteinuria, BUN, and serum creatinine levels in a 59-year-old white female

Date	*24-h Proteinuria (mg)*	*BUN (mg/ dL)*	*Serum Creatinine (mg/dL)*
June 25, 2005	5010		
September 30, 2005		45	4.1
October 2, 2005	3071	61	5.7
Home medication: glyburide, lisinopril, amlodipine			
BUN increased by 16 mg/dL and serum creatinine increased by 1.6 mg/dL in 3 days.			
Lisinopril was discontinued and bicarbonate infusion was started by the author. Author was on-call nephrologist. However, the patient's regular nephrologist started her on hemodialysis treatment.			

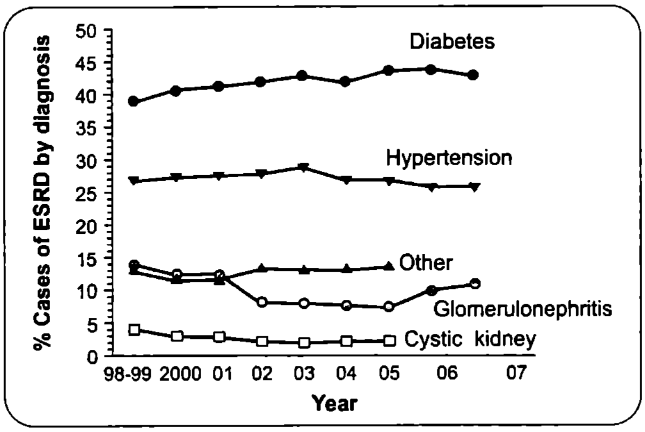

Figure 1: Percentage of end stage renal disease (ESRD) by diagnosis. Diabetes remains the main cause of ESRD. Adapted from the US Renal Data System (USRDS, 2007)

was normal to slightly impaired. Of the 37 patients followed for at least five years, 24 (65 percent) had complete or partial remission of proteinuria; in 6 others (16 percent), ESRD developed, and they required dialysis. As calculated by the Kaplan-Meier method, the estimated probability of retaining adequate kidney function was 88 ± 5 percent after five years and 73 ± 7 percent after eight years. The authors concluded that most untreated patients with idiopathic membranous nephropathy maintain renal function for prolonged periods and are likely to have spontaneous remission of proteinuria.

2. A 20-year follow-up evaluation of young men with fixed and reproducible orthostatic proteinuria showed no evidence of progressive renal disease. Follow-up information was obtained in 43 of the original 64 patients. All had normal renal function and only 6 patients continued to show qualitative proteinuria. The authors concluded that the 20-year prognosis of patients with fixed and reproducible orthostatic proteinuria was excellent.

These two studies are provocative of our contention that proteinuria, including nephrotic-range proteinuria, has no adverse effect on renal function. The following case studies will further attest to that hypothesis.

CASE STUDIES FROM THE AUTHORS' EXPERIENCE

Case 1: Nondiabetic Renal Disease

A 59-year-old white male was first seen in the office by one of the authors (AKM) on February 7, 2005, as a self-referral for swelling of the ankle and low blood count. Both his sitting and standing blood pressure (BP) were 130/80 mmHg. During preparation for gastrointestinal endoscopy, he was noted to have proteinuria and hence referred to a nephrologist. On December 15, 2004, his 24h proteinuria was 8119 mg and Ccl 80 ml/min. A percutaneous kidney biopsy was done; the histopathology findings were consistent with lipoprotein nephropathy. His medication at the time of his first office visit with the author included allopurinol 300 mg po daily, lisinopril 5 mg po twice daily, Tricor® 48 mg po once daily, Lipitor® 10 mg po daily, aspirin and fish oil tablets. He denied history of diabetes or hypertension. He does not smoke or drink alcohol.

A serum chemistry on January 25, 2005, revealed creatinine 1.6 mg/dL, Na^+ 142 mmol/L, K^+ 4.5 mmol/L, chloride 108 mmol/L, CO_2 27 mmol/L, calcium 8.7 mg/dL, total protein 5.5 g/dL, albumin 3.3 g/dL, lipoprotein 22 mg/dL, triglyceride 500 mg/dL, total cholesterol 263 mg/dL, glucose 100 mg/dL. His hemoglobin and hematocrit were 11.2 g/dL and 32.5 percent, respectively. Microalbumin/creatinine ratio was 1330. A 24h urinary protein was 1901 mg. During the first office visit, lisinopril was discontinued. Other medications were continued. Atenolol (Tenormin®) 25 mg once daily was prescribed to keep BP under control. Serial 24h proteinuria, serum creatinine, and Ccl from December 15, 2004, through September 30, 2010 (70 months), are presented in Table 2. As one can see in Table 2, his serum creatinine level decreased and remained within a normal range throughout the reminder of the years. Likewise his Ccl increased and remained in the normal range. Proteinuria remained essentially unchanged except for several episodes of higher proteinuria on April 7, 2005, and July 27, 2007, and most recently in January, 2010. Proteinuria is again decreased in a sample taken September 30, 2010. Most importantly, his renal function did not decline despite persistent proteinuria. Furthermore, his serum albumin is stable at 3.4 g/dL and better than his serum albumin of 3.3 g/dL 70 months ago.

Case Studies of Patients with Diabetes Associated with Proteinuria and Chronic Kidney Disease

The aim here is to illustrate the impact that elevated blood glucose levels have on renal function and proteinuria and how glucose control mitigates these complications. Also, these presentations will reveal that attempts to reduce proteinuria with manipulations other than glucose control is associated with adverse effects on renal function.

Case 2

A 67-year-old African-American female was referred to one of the authors (AKM) for decreased Ccl. She gave a history of diabetes mellitus for 12 years. She was prescribed fosinopril (ACEI) to reduce proteinuria. After five years of fosinopril treatment, her proteinuria decreased to almost undetectable levels but paralleled a decrease in Ccl of 56 percent. During this time period, SCr increased slightly but remained within the normal laboratory range. Fosinopril was discontinued. After fosinopril discontinuation, she had slight proteinuria but a normal Ccl. She takes hydralazine 25 mg three times daily, amlodipine 5 mg daily, atenolol 25 mg once daily, a combination of triamterene and hydrochlorothiazide 37.5 mg / 25 mg once daily for BP control, and glyburide 5 mg daily for glucose control. Her glucose and BP control are optimum. SCr ranges between 0.7 to 1 mg in every office visit (Table 3).

Case 3

A 65-year-old white male had a history of diabetes mellitus for 23 years. Although he was treated with Humulin N(insulin), his glucose control was not adequate. In October 2001, his fasting glucose was 203 mg/dL, and he had hard exudates and microaneurysms in the left eye. He was placed on enalapril po 10 mg daily for heavy proteinuria in October 2001. Proteinuria was 8324 mg/24h and his Ccl was 87 ml/min as of December 2001. Discontinuation of enalapril in December 2001 resulted in an increase in proteinuria to 13476 mg/24h and Ccl to 105 ml/min when measured in January 2002. SCr was 2.0 mg/dL. Enalapril 5 mg po daily was reinstituted and was subsequently increased to 20 mg daily. On November 2002, proteinuria decreased to 6443 mg/24h and Ccl to 59 ml/min, while SCr was 2.5 mg/dL. Enalapril was discontinued. Again his proteinuria increased to 13813 mg/24h but Ccl increased only modestly to 76 ml/min, while SCr decreased to 2.4 mg/dL. Enalapril 10 mg daily was reinstituted. On February 28, 2003, his proteinuria decreased again to 6048 mg/24h as did Ccl to 46.2 ml/min. SCr increased to 2.8 mg/dL. Enalapril was discontinued. In March 2003, he refused to take enalapril any further. He controlled his glucose with insulin injections several times daily; his BP with diltiazem 240 mg twice daily and amlodipine 5 mg once daily. On April 19, 2005, his proteinuria decreased to 2209 mg/24h; Ccl remained unchanged at 46 ml/min.

Table 2. Serially 24h proteinuria, creatinine clearance, and serum creatinine levels in a 59-year-old white male with lipoprotein nephropathy

Date 2004-2007	*24h Proteinuria (mg)*	*24h Ccl/ eGFR (ml/min)*	*Serum Creatinine (mg/dL)*
December 15, 2004	8119	80	1.5
January 25, 2005	1901	NA	1.6
Lisinopril discontinued			
April 7, 2005	2920	96	1.5
August 15, 2005*	1144	77	1.7
Pentoxifylline 400 mg po twice daily			
November 7, 2005	1290	87	1.5
April 12, 2006	1316	104	1.3
Pentoxifylline reduced to 400 mg po once daily			
January 19, 2007	ND	eGFR >60	1.2
Dizziness; Flomax® changed to doxazosin 1 mg po once daily			
June 20, 2007	1853	105	1.3
July 27, 2007	2805	117.6	1.3
August 11, 2008	1949	104	1.3
April 9, 2009	1470	81	1.1
Medication: doxazosin 4 mg daily; metoprolol 25 mg daily; pentoxifylline 400 mg x 1 daily; allopurinol 150 mg daily; Lipitor® 20 mg daily; AcepHex® 20 mg daily			
January 11, 2010	5729	97.6	1.4
February 23, 2010	3337	82	1.3
September 30, 2010	2387	139.8/67.8	1.1

ND = not done; NA = not available.

* = urinary frequency and Strangury associated with enlarged prostate. He was treated with Flomax® by a urologist. Subsequently, urinary symptoms were reduced to minimal.

Table 3. Effect of fosinopril on proteinuria and renal function in a 67-year-old African-American female with a 12-year history of diabetes

Date 1999-2006	*24h Proteinuria (mg)*	*24 Ccl (ml/ min)*	*Serum Creatinine (mg/dL)*
October 17, 1999	160	125	0.8
Fosinopril 20 mg daily started			
November 9, 2000	88	90	0.9
December 8, 2002	142	81	1.0
February 18, 2004	5	55	1.1
Fosinopril discontinued			
July 15, 2004	151	96	1.0
January 20, 2005	417	76	1.0
April 7, 2005	215	86	0.9
June 8, 2006	257	70	0.7
December 11, 2006	<150	80	1.0

Ccl = creatinine clearance.

SCr decreased slightly to 2.5 mg/dL. On March 27, 2006, his proteinuria decreased further to 2070 mg/24h and Ccl increased to 50 ml/min. SCr was essentially unchanged at 2.6 mg/dL. His fasting glucose was 102 mg/dL and 2h-postprandial glucose was 143 mg/dL. HbA1c was 7.9 percent. In 2007, his HbA1c ranged between 6.4 and 6.5 percent, suggesting good glucose control. On December 3, 2007, his fasting and 2h postprandial blood glucose levels were 103 mg/dL and 116 mg/dL, respectively. His serum creatinine was 2.5 mg/dL, which was unchanged from 2005. A 24h Ccl was 47.1 ml/min, but 24h proteinuria increased to 4934 mg. He felt fine and energetic and worked full time in his business. On August 4, 2008, 24h proteinuria was 4031 mg, and Ccl was 40.7 ml/min. On October 20, 2008, an unknown physician prescribed lisinopril 2.5 mg po and furosemide 40 mg twice daily, which he continued to take until November 7, 2008. On November 5, 2008, his 24h proteinuria decreased to 2369 mg with a parallel decrease in Ccl to 22.6 ml/min. Serum creatinine increased to 3.89 mg/dL (Fig. 2). Eighteen days after discontinuation of lisinopril and furosemide, his 24h proteinuria again increased to 4244 mg and Ccl to 37.5 ml/min. Serum creatinine decreased to 2.9 mg/dL. Since then his serum creatinine has slowly increased and his eGFR ranges between 12 and 15 ml/min in each visit. He is essentially asymptomatic.

Case 4

A 53-year-old white male had his first office visit with one of the authors (AKM) on November 8, 2007, referred by a primary care physician for renal insufficiency. He gave a history of diabetes for 37 years and had always been treated with insulin. He had coronary artery bypass graft surgery in March 1999. He received enalapril 10 to 20 mg po daily since 1990. He has diabetic retinopathy with markedly decreased vision in the left eye. He had a right foot ulcer that is healed. His serial 24h proteinuria and Ccl are presented in Table 4. His serial serum glucose levels are correlated with eGFR (Fig. 3). These results show a significant negative correlation between serum glucose levels and eGFR. The higher the glucose level above 200 mg/dL, the more severe is the renal function impairment. This relationship, between elevated blood glucose levels above 200 mg/dL and increased SCr or decreased eGFR, is shown in two additional patients (Tables 5 and 6).

Case 5

A 67-year-old African-American female gave a long history of diabetes and treatment with insulin. On September 10, 2007, her 24h Ccl was 83.0 ml/min and 24h proteinuria was 142 mg. Findings from an office visit on November 3, 2007, are presented (Table 5). It is evident that the 2h postprandial glucose level above 200 mg/dL

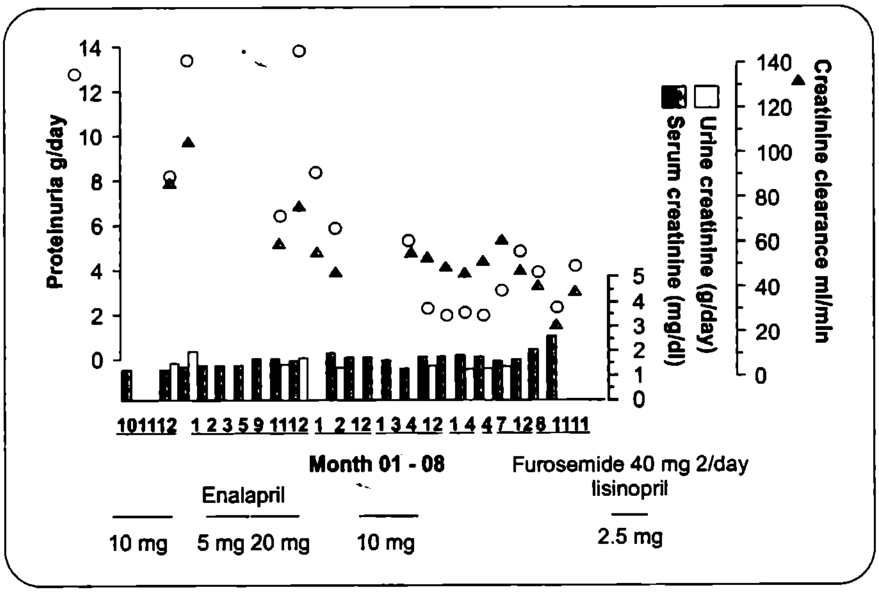

Figure 2: Proteinuria, creatinine clearance, and urine and serum creatinine in a patient before and after treatment with an ACEI

is accompanied by elevated BUN and serum creatinine and reduction of eGFR.

Case 6

Laboratory studies in a 91-year-old white male, admitted to hospital with acute renal failure, hyperkalemia, and metabolic acidosis associated with lisinopril, are shown in Table 6. Discontinuation of lisinopril and bicarbonate infusion resulted in reversal of the abnormalities. The patient had no known history of diabetes; however, the glucose levels close to and above 200 mg/dL indicate that the patient has diabetes.

The correlation between proteinuria and Ccl was calculated on data found from patients 3 and 4 (Fig. 4). There was a significant positive correlation between these two variables; the higher the proteinuria, the higher is the Ccl. These findings could be seen in individual patients where proteinuria varied throughout their treatment period.

OVERALL COMMENTS FROM THE CASE FINDINGS

Evidence from the older literature before the use of ACEI/ARB as well as the authors, own clinical observations indicate that proteinuria, including heavy proteinuria, is not adverse to renal function (Tables 1 through 4). On the other hand, manipulation of proteinuria with ACEI or ARB is associated with a decline of renal function (Table 3, Figs 2 and 4). It is evident in our study that ACEI causes a parallel reduction of proteinuria and Ccl, suggesting that proteinuria is reduced relative to reduction of renal function. There is no discernible mechanism thus far identified by which ACEI or ARB therapy can reduce proteinuria, except by reducing the glomerular filtration rate.

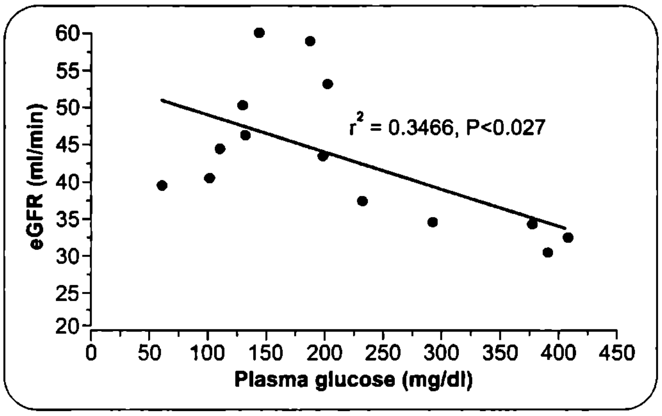

Figure 3: Correlation between serum glucose levels and eGFR in a diabetic patient. A significant negative correlation exists between eGFR and serum glucose levels. This negative correlation is most obvious when serum glucose is greater than 200 mg/dL

Table 4. Serial laboratory studies in a 53-year-old male with a very long history of diabetes mellitus

Date (yy/mm/dd)	*Ccl (ml/min)*	*24-h Proteinuria (mg)*
07/11/08	NA	2378
	Enalapril discontinued	
07/11/23	Admitted to hospital for cough and shortness of breath: Solu-Medrol (methylprednisolone) 60 mg IV every 6h.	
07/11/24	39.4	
07/11/26	Methylprednisolone discontinued	
08/01/10	42	3725
08/05/19	57.7	3737
08/09/19	51.1	2948
08/11/24	56.6	4587

NA = not available.

Table 5. Laboratory studies in a 67-year-old African-American female with a long history of diabetes and treated with insulin

Chemistry Panel November 3, 2007	*Time (status) 7:11 am (F)*	*Time (status) 10:00 am (2h PP)*
Glucose (mg/dL)	109	232
BUN (Mg/dL)	16	19
SCr (mg/dL)	1.28	1.49
eGFR (ml/min)	44	37
Na^+ (mmol/L)	141	139
K^+ (mmol/L)	3.8	5.0
CO_2 (mmol/L)	27	22

October 01, 05, SCr 1.3, Lotrel® (a combination of amlodipine and benazepril) discontinued.

F = fasting; 2hPP = 2-hour postprandial' SCr = serum creatinine.

Other studies have raised doubts as to whether and to what extent these approaches, i.e., treatment with ACEI/ARB or a combination of both, actually slows down diabetic nephropathy progression and ESRD risk. In other words, it is questionable whether reduction in proteinuria as a surrogate end point translates into long-term benefit in the prevention of chronic kidney disease. Systematic reviews and meta-analysis concluded that adding an ARB to an ACEI further reduced proteinuria in diabetic nephropathy by a mean of approximately 200 mg/dL, but studies of long-term outcomes are still needed.

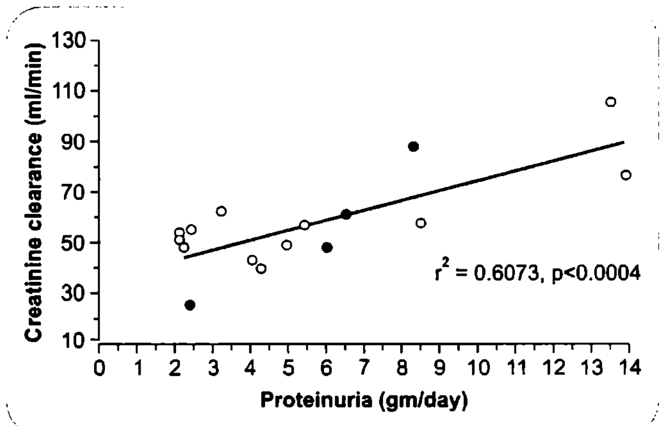

Figure 4: Correlation between proteinuria and creatinine clearance in two diabetic patients. Closed circles indicate when the patients were taking ACEIs, while open circles indicate when the patients were off ACEI. A significant positive correlation is seen indicating that when proteinuria is reduced so is creatinine clearance

An important mechanism of proteinuria is loss of heparan sulfate (HS) proteoglycan from the glomerular basement membrane. Previous studies have shown that removal of HS has resulted in increased permeability of the glomerular basement membrane to albumin. There is evidence that hyperglycemia leads to a downregulation of HS synthesis accompanied by a reduction in the degree of HS sulfation. Loss of glomerular HS has been reported in renal diseases with proteinuria, including diabetic nephropathy, minimal change disease, and membranous nephropathy.

Experimental studies from our laboratory reveal that treatment of porcine vascular endothelial cells with high glucose (540 mg/dL) upregulates the expression of heparanase, a HS-degrading endoglycosidase. Heparanase degrades HS and could lead to proteinuria. Other studies have found that heparanase-1 was upregulated in the renal epithelial cells in the kidney with diabetic nephropathy. Even in the clinical setting, subcutaneous injection of heparin, a polyanion similar to HS, decreased proteinuria in Type 1 diabetes mellitus, suggesting a role of HS in diabetic nephropathy. Thus, it is prudent to state that proteinuria in diabetic and nondiabetic renal diseases may be due to deficiency of HS in the glomerular basement membrane as a result of heparanase overexpression and degradation of HS. Further investigation in this area is essential to elucidate the role of the glomerular basement membrane HS in

Table 6. Laboratory studies in a 91-year-old white male admitted to hospital for acute renal failure, hyperkalemia, and metabolic acidosis associated with lisinopril

	November 29, 2007		*November 30, 2007**	
Chemistry Panel	*Time (status)* 5:08 am (F)*	*Time (status) 10:20 am (2hPP)*	*Time (status) 5:00 am (F)*	*Time (status) 10:05 am (2hPP)*
Glucose (mg/dL)	129	202	142	187
BUN (mg/dL)	32	33	29	30
SCr (mg/dL)	1.19	1.34	1.20	1.23
eGFR (ml/min)	>60	53	60	59
Na^+ (mmol/L)	147	146	145	144
K^+ (mmol/L)	4.5	4.6	4.9	4.9
CO_2 (mmol/L)	24	25	23	26

F = fasting; 2hPP = 2-hour postprandial; SCr = serum creatinine; eGFR = estimated GFR; HbA1c 6.1%.
* Following bicarbonate infusion and discontinuation of lisinopril

the evolution of progressive proteinuria and glomerular sclerosis.

In diabetes, proteinuria relates to uncontrolled hyperglycemia. Poor glycemic control correlates with hyperfiltration and renal hyperperfusion in Type 1 diabetes mellitus. From this study, an argument can be advanced that good glycemic control with intensive insulin therapy can reduce glomerular hyperfiltration and loss of HS, and hence proteinuria. It should be noted that normalization of blood glucose levels in advanced stages of diabetic nephropathy, as in patient #3 (Fig. 2), may not necessarily meliorate proteinuria, suggesting a secondary, albeit important, mechanism, such as HS loss induced by hyperglycemia. A study from Geneva, Switzerland, consisting of 510 diabetic patients, reports that adequate glycemic control (2-h postprandial <200 mg/dL) ameliorates proteinuria; most patients maintained adequate GFR even though proteinuria had been recorded for many years. The Heart Outcomes Prevention study (HOPE) investigated the relationship between fasting plasma glucose and incident cardiovascular outcomes, death, heart failure, and overt nephropathy in diabetic and nondiabetic individuals. Results show that 1 mM (18 mg/dL) rise in fasting plasma glucose was related to an increased risk in cardiovascular outcomes, death, heart failure, and overt nephropathy. This study further stressed that there is an independent progressive relationship between indices of glycemia and incident cardiovascular events, renal disease, and death. Normalization of blood glucose for any appreciable period of time is difficult to achieve. We have demonstrated that serum glucose levels are negatively and significantly correlated with renal function represented by eGFR; the higher the serum glucose, the lower the eGFR (Fig. 3). Therefore, 2h postprandial glucose control to less than 200 mg/dL, is essential to protect renal function. Clinical trials of glucose lowering alone to prevent this outcome in diabetic and nondiabetic individuals are indicated.

Notwithstanding abundant evidence in support of glycemic control as a central factor to mitigate proteinuria and protect renal function, excessive enthusiasm to treat proteinuria, including microalbuminuria, with ACEI or ARB still prevails. A most recent collaborative multicenter study dampens that enthusiasm. This study revealed that proteinuria by itself cannot be taken as a definite marker of improved renal function. Combination therapy of ACEI and ARB reduces proteinuria to a greater extent than monotherapy, but overall renin-angiotensin inhibitor therapy adversely affects renal outcomes. These findings are in agreement with our hypothesis. As well, a recent editorial has addressed the problems of using ACEI, ARB, or combination therapy. This article states that in view of the risks of hyperkalemia, hypotension, and perhaps even worsening renal function, more data from carefully designed trials are needed before the general medical community widely applies a complete blockade of the renin-angiotension-aldosterone pathway to prevent progressive kidney disease. Finally both the multicenter trial and the editorial are supportive of the authors' observations on the harmful effects of ACEI/ARB to treat proteinuria.

KEY POINTS

1. Pathophysiology of proteinuria in diabetic and nondiabetic renal diseases is not yet fully elucidated.
2. Previous studies in membranous glomerulonephritis have shown that proteinuria remits spontaneously and does not reduce survival.
3. There is no substantive evidence that proteinuria has a direct effect on renal function.
4. There is increasing obsession in current medical practice to reduce proteinuria using ACEI, ARB, or a combination of both groups of drugs.
5. The above drugs reduce proteinuria but only at the expense of decrease in renal clearance. There is no magic mechanism discerned by which ACEI/ARB reduce proteinuria.
6. The goal to reduce the incidence of ESRD in diabetic and nondiabetic renal diseases by reducing proteinuria has not been met.
7. The authors strongly feel that proteinuria per se does not need manipulation except glycemic control in diabetes.
8. The authors recommend treatment of primary problem, such as glucose control in diabetes or immunosuppressive therapy in immunologic disorders.
9. The area of glomerular basement membrane heparan sulfate in the understanding and management of proteinuria needs elucidation.

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21

Cystic Diseases of the Kidney

Anil K Agarwal, Soni Dhanireddy

Renal cysts develop from different parts of nephron, are lined by renal epithelium and the fluid often resembles tubular fluid. Cysts eventually become disconnected from the part of the tubule they develop from. The cysts are filled with fluid or debris. Enlargement of cysts, as in polycystic kidney disease, can lead to anatomical distortion of renal parenchyma, abdominal wall enlargement, pain and renal insufficiency. Simple cysts are usually asymptomatic and do not cause renal insufficiency.

Cysts may be present in one or both kidneys and can be solitary or multiple. Presence of a family history or co-existing developmental abnormalities may indicate presence of a hereditary syndrome. Presence of cysts is most often detected by routine radiologic tests. Further evaluation of the cysts may be required due to the presence of renal insufficiency, concerns with polycystic kidney disease or due to atypical features suggestive of malignancy.

Cystic diseases of the kidney can be classified as simple cysts, hereditary cystic diseases, acquired cystic disease and cysts with location in the pelvis, hilum and perinephric regions of the kidney (Table 1). Important cystic diseases along with their clinical features, associated gene and frequency are summarized in Table 2.

SIMPLE CYSTS

Simple cysts are present in up to 50 percent of the population above the age of 50 years, making this condition the most common form of the cystic disease of the kidney. Prevalence of cysts increases with age and has been noted to be higher in those with presence of urinary tract obstruction. Cysts may be present in one or both kidneys and are not inherited. Cysts can vary in size, are usually uni-locular and have thin walls. Simple cysts are uncommon in patients younger than age 30, and are rarely multiple or bilateral.

Table 1. Cystic diseases of kidney

Simple cysts	
Hereditary cystic diseases	
	Autosomal dominant polycystic kidney disease (ADPKD)
	Autosomal recessive polycystic kidney disease (ARPKD)
	Tuberous sclerosis
	Von Hippel-Lindau syndrome
Medullary cysts	
	Medullary cystic disease (MCD)
	Medullary sponge kidney (MSK)
Acquired cystic kidney disease (ACKD)	
Miscellaneous cystic diseases	
	Cystic renal dysplasia
	Multilocular cyst
	Pyelocalyceal cyst
	Hilar cyst
	Perinehric pseudocyst
	Renal lymphangiomatosis

Table 2. Summary of cystic diseases of the kidney

	Clinical Onset (yrs)	*Cysts*	*Renal Function*	*Nephrolithiasis*	*Disease Gene*	*Frequency*
ADPKD	30-40	Multiple	Normal, Impaired	Common	PKD1, PKD2	1:400-1000
ARPKD	Perinatal	Multiple	Normal, Impaired	Nephrocalcinosis	PKHD1	1:10,000-40,000
MCD	Variable	Few, Multiple	Normal, Impaired	No	NPHP1-NPHP5	34-56 new cases/yr
MSK	20-40	Multiple	Normal	Common	None	1:5,000-20,000
TS	10-30	Multiple	Normal, Increased	No	TSC1, TSC2	1:10,000
VHL	30-40	Few, Bilateral	Normal, Increased	No	VHL	1:36,000
Simple Cysts	>40	Single, Multiple	Normal	No	None	Increases with Age
ACKD	Variable (Chronic Renal Failure)	Multiple	Impaired, ESRD	No	None	7-22% patients with CKD

ADPKD = Autosomal Dominant Polycystic Kidney Disease; ARPKD = Autosomal Recessive Polycystic Kidney Disease; MCD = Medullary Cystic Kidney Disease; MSK = Medullary Sponge Kidney; TS = Tuberous Sclerosis; VHL = Von Hippel-Lindau; ACKD = Acquired Cystic Kidney Disease.

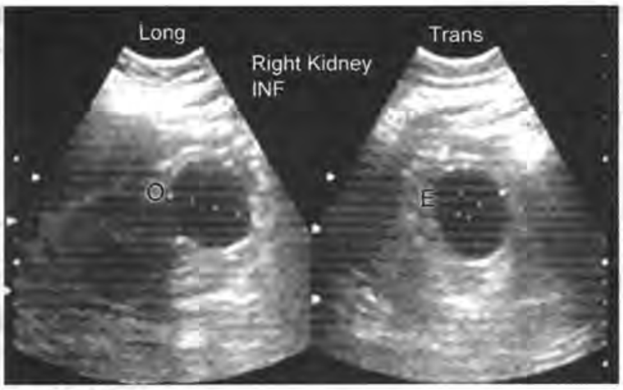

Figure 1: Ultrasound of the kidney showing a simple renal cyst in longitudinal and transverse axis. The walls are smooth, well differentiated from surrounding parenchyma and there are no internal echoes

Clinical Features

Cysts mostly present as an incidental finding on abdominal CT scan or ultrasound (Fig. 1). Sometimes they can present due to hematuria, especially after flank injury. Rarely, they can present with features of infection or hypertension. There is no evidence that simple cysts cause renal insufficiency.

Diagnosis

Majority of simple cysts do not need extensive evaluation and can be followed periodically with radiologic imaging, depending upon their characteristics. Evaluation of simple cysts with atypical features can be accomplished by abdominal ultrasound, CT or MRI with due caution when using contrast media if renal insufficiency is present. Simple cysts are likely to have thin, homogeneous, regular walls, and low echogenicity with ultrasound, as compared to thick, heterogeneous and irregular walls and high echogenicity in case of complex cysts (Table 3). Aspiration of hemorrhagic fluid that shows atypical cells may suggest malignancy, but aspiration of fluid for this purpose is not recommended.

Table 3. Differentiation of simple cyst from malignancy (by contrast enhanced CT or US)

Cyst characteristic	*Simple Cyst*	*Malignancy*
CT		
Cyst wall	Thin	Thick
Attenuation	Homogeneous (near water density)	Heterogeneous, may be solid
Contrast enhancement	No	Yes
Interface with surroundings	Smooth	Irregular
Calcification	Usually none (in 2% only), or peripheral	Central
Ultrasound		
Echogenicity	Echolucent	Echogenic
Aspiration		
Cyst fluid	Straw-colored, clear	Dark or bloody
Cytology	no atypical cells on microscopy	Elevated lipids and cholesterol Malignant cells on microscopy

Treatment

Treatment of simple cysts is usually not required. For large, symptomatic cysts, percutaneous drainage can be helpful. Some cases may require surgical drainage and sclerotherapy with instillation of alcohol. Infected cysts can be treated with antibiotics that are lipid soluble, but surgical removal of cyst may be required in intractable cases.

POLYCYSTIC KIDNEY DISEASE

Polycystic diseases of the kidneys are characterized by the presence of innumerable cysts in both kidneys, involving both the cortex and the medulla. Autosomal dominant polycystic kidney disease (ADPKD) is the most common variety. Since it can be found at all ages, it should not be called adult polycystic kidney disease. Autosomal Recessive Polycystic Kidney Disease (ARPKD) is less common and occurs at a younger age, often in neonates and infants.

Autosomal Dominant Polycystic Kidney Disease

ADPKD is one of the most common hereditary diseases, occurring in 1 out of 400 to 1000 live births. It affects over half a million people in the United States and more than 12.5 million families globally. In the United States, it is responsible for about 7 percent of the end stage renal disease (ESRD) population on dialysis and 10 percent of those with renal transplant. It is more common than cystic fibrosis, sickle cell disease, hemophilia, Down's syndrome and muscular dystrophy combined.

About 85 to 90 percent of the cases of ADPKD occur due to mutation of the PKD1 gene on chromosome 16, and are responsible for coding the protein Polycystin-1. About 10 to 15 percent of clinically detected cases are due to mutations of PKD2 gene on chromosome 4, encoding Polycystin-2. Polycystin-1 is localized in renal tubular epithelia, hepatic bile ducts, and pancreatic ducts. It is involved in adhesive protein-protein, cell-cell, and cell-matrix interactions. Polycystin-2 is expressed in distal tubule, cortical collecting tubule, and thick ascending loop of Henle cells. It is involved in cell calcium signaling. Mutations of polycystin-1 and polycystin-2 seem to affect fluid secretion into the cysts, abnormal cell growth and accelerated apoptosis of epithelial cells. Although the mutation is present in all tubular cells in the kidney, cysts form in only about 5 percent of nephrons. It is believed that a "double hit," involving mutations in both the germ line (mutation inherited from a parent) and the somatic cell, is necessary to fully express the disease. Cysts arise mostly from tubular segments and later become disconnected from them.

ADPKD can occur at any age and affects all races and both sexes, although males tend to manifest slightly more severe disease. Although cysts can be present at young age, the clinical presentation is usually in the fourth or fifth decade. The mean age of onset of symptoms, diagnosis and death is 41 years, 47 years, and 52 years, respectively. The expression of clinical disease becomes more apparent with increasing age. It was believed that the natural history of the disease within a family followed similar pattern, but that has not been proved to be the case. About 60 percent of the patients with PKD develop renal failure.

Clinical Features

The most common presenting symptom of ADPKD is flank pain in about 60 percent of the adults and a third of the children. The flank pain may be related to presence of large kidneys causing continuous, disabling pain. In others, pain can be precipitated by trauma to the flank causing rupture of a cyst. Infection in a cyst and presence of urinary stone can also cause flank pain. About half of the patients develop hematuria, which may be gross or microscopic. Recurrent urinary tract infections can occur in a third of patients, and may be associated with urinary obstruction from a stone or large cyst. Abdominal mass may be present due to enlarged kidneys or enlarged liver. Renal insufficiency is common. Anemia tends to develop late due to inadequate erythropoietin production from enlarged kidneys. Routine imaging or screening of family members can detect presence of disease in some patients. In some patients, extra renal manifestations, such as intracranial bleeding from an aneurysm, can be the presenting and dominating features.

Renal Manifestations

ADPKD is characterized by the presence of enlarged kidneys bilaterally with presence of innumerable cysts that vary in size from few millimeters to several centimeters (Fig. 2). Significant proteinuria is uncommon and nephrolithiasis occurs with higher frequency. Hypertension is common, correlates with size of cysts and is more severe in the presence of renal insufficiency. Renal insufficiency can be variable in onset, progresses with age and appears later in PKD2 than in PKD1. The rate of decline in renal function is usually linear in the absence of other complications. Dialysis may be required in about a third of the patients by the age of 60 years. Early age of presentation, large kidneys, onset of hypertension before age 35, moderate proteinuria, male sex and black race are associated with greater risk of deterioration of renal function. Presence of ADPKD-1 gene, DD allele of angiotensin converting enzyme (ACE) and sickle hemoglobin are additional risk factors for worsening of renal function. Presence of cystic fibrosis gene may cause the disease to be milder.

Renal cell carcinoma is not more common in ADPKD than in general population, but is difficult to diagnose. It is more likely to be bilateral and associated with fever.

Extrarenal Manifestations

Polycystin-1 and Polycystin-2 are expressed in many organs causing multisystem abnormalities in PKD (Table 4). The most common manifestations and their management are described in the management section.

Diagnosis

Choice of the method of imaging for polycystic kidney disease is important, since the number and size of the cysts varies according to the age. Renal ultrasound has the advantage of avoiding radiation or contrast administration, and can detect cysts of about 1 cm size. It can miss small cysts and is operator dependent. In ADPKD-1, almost 100 percent of the patients above the age of 30 years can be diagnosed by ultrasound. The guidelines require presence of at least 2 cysts (either unilateral or bilateral) in patients younger than age 30, at least 2 cysts in each kidney between 30 to 59 years of age, and at least 4 cysts in each kidney in patients older than age 60 for the diagnosis of ADPKD-1. Thus, absence of cysts by ultrasound after 30 years of age nearly rules out the presence of ADPKD-1. While these criteria may not apply to other polycystic kidney diseases (ADPKD-2 and ARPKD) due to their slower progression, absence of cysts at 30 years of age predicts less likelihood of severe renal insufficiency. CT with contrast and MRI with contrast have better sensitivity and can be used in younger patients. They can also detect the presence of cysts in other organs, and can differentiate between solid and cystic masses. Abdominal CT with contrast or MRI with gadolinium should be performed in potential kidney donors who are younger than 30 years of age and

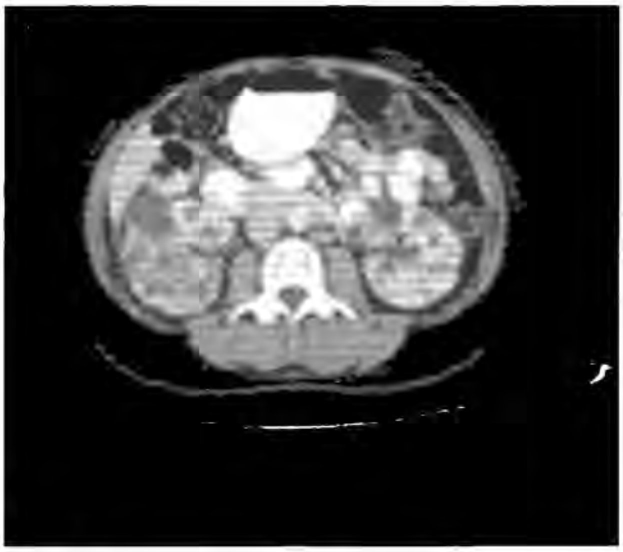

Figure 2: CT scan of abdomen showing bilateral multiple cysts of varying size present in enlarged kidneys, diagnostic of polycystic kidney disease

Table 4. Extrarenal manifestations of ADPKD

Cardiovascular:	Hypertension
	Diastolic dysfunction
	Valvular regurgitation
	Mitral valve prolapse
	Intracranial aneurysms
	Aortic root dilatation and aneurysm (thoracic or abdominal)
	Arterial dolichoectasias
	Arterial dissections (intracerebral, aortic, coronary, iliac, splenic)
Gastrointestinal:	Hepatic cysts
	Rarely cholangiocarcinoma, congenital heaptic fibrosis
	Pancreatic cysts
	Colonic diverticuli
Miscellaneous Cysts:	Ovary
	Seminal vesicle, epididymis
	Arachnoid
	Pineal
	Spleen
Musculoskeletal:	Hernia formation

gene linkage analysis can be used in potential kidney donors with indeterminate diagnosis by imaging studies. Gene linkage analysis requires at least three affected members in a family for analysis, and this may not be possible in some families. In up to 25 percent of cases there is no family history. Direct mutation analysis of the PKD1 and PKD2 genes are also available, however, most mutations are unique or missense mutations that may be difficult to detect. Presymptomatic screening before age 20 may not be conclusive and ADPD2 patients tend to manifest disease at a later age, so screening is generally not recommended for patients younger than age 20. Presymptomatic screening should be offered with caution as this may affect insurability and employment, however, if ADPKD is diagnosed, the patient can receive appropriate genetic counseling and early intervention if required.

Management

Available methods of treating PKD are directed towards preservation of renal function, and management of associated complications. Many experimental therapies to reduce the growth of cysts have shown promise in animal studies, but human studies are lacking at this time.

Preservation of Renal Function

1. Intensive management of hypertension is critical. It has been proposed that aggressive control of blood pressure can delay the onset of ESRD by about 15 years. ACE inhibitors are recommended in decreasing proteinuria if present, but should be used with caution in the presence of advanced renal insufficiency, markedly enlarged kidneys and sodium depletion. The HALT-PKD study is ongoing and aims to study whether the combination of ACE-I and ARB is superior to ACE-I alone in delaying disease progression. The study also investigates whether a low BP target is superior to a standard BP target in patients with preserved renal function.
2. Role of dietary restriction of protein is not established, though a low protein diet may be helpful. Modification of Diet in Renal Disease (MDRD) study, which had enrolled a significant number of patients with PKD, showed 29 percent reduction in rate of decline in renal function, just short of the statistical significance of 30 percent.
3. Caffeine restriction is considered helpful in reducing enlargement of cysts due to less activation of cyclic AMP, but is not well established. Similarly, potassium citrate administration has been shown to be beneficial in animal models, but not proven in humans.
4. Hypokalemia can promote development of cysts and should be adequately treated.
5. Nephrotoxic agents including nonsteroidal agents should be avoided.
6. Physical injury to the kidneys as well as instrumentation of urinary tract should be avoided.

Treatment of Complications

Pain, intrarenal bleeding and hematuria can be managed with bed rest, analgesics and hydration. Persistent pain, or pain associated with weight loss, anemia and fever may indicate infection, stone or tumor which should be looked for in appropriate circumstances. For persistent and severe bleeding intra-arterial injection of gelfoam has been used successfully during angiography.

Large cysts and stones can be managed with minimally invasive surgery or open surgery. Cyst drainage, sclerosis and marsupialization can be done. Cyst decompression is again emerging as a palliative therapy for large cysts with intractable pain, and does not seem to be particularly harmful. Renal denervation is an option for intractable pain related to numerous small cysts. Nephrectomy can be done as a last resort. Transcatheter renal artery embolization has been used to decrease the size of the kidney in a dialysis patient.

Urinary tract infections are more common in females and are usually caused by Gram-negative organisms. The route of infection is usually retrograde from the bladder and cystitis and asymptomatic bacteriuria should be treated promptly in ADPKD patients to avoid retrograde seeding of the renal parenchyma. Presence of flank tenderness, negative urine culture with or without positive blood cultures and failure of usual antibiotic therapy of urinary tract infection indicate presence of cyst infection. Antibiotics with high lipid solubility and a high pKa (such as trimethoprim-sulphamethoxazole, ciprofloxacin, erythromycin, clindamycin and tetracycline) can achieve high concentration in cyst fluid. The agents of choice in outpatient management include Trimethoprim-sulfamethoxazole and fluoroquinolones. Antibiotics may have to be used for prolonged period, and if fever persists after two weeks of appropriate antibiotic therapy, surgical drainage of infected cyst may be necessary.

Renal stones occur in approximately 20 percent of the patients with ADPKD and mostly comprise of calcium oxalate or uric acid. The pathogenesis of stone formation is thought to be urinary stasis due to distorted renal anatomy. The stones can cause recurrent infections or obstruction. Management includes maintenance of adequate fluid intake, potassium citrate supplementation for hypocitraturia, thiazide diuretics for hypercalciuria and allopurinol for hyperuricosuria. Larger stones that cannot pass spontaneously generally require extracorporeal shock wave lithotripsy (ESWL) or percutaneous nephrolithotomy (PCNL).

Renal cell cancer is not excessively common in these patients, though renal adenoma is more common. Periodic follow up is required in suspicious cases.

Nephrectomy is an extreme measure that should be reserved for management of uncontrollable hemorrhage, intractable pain, recalcitrant infection and recurrent obstruction due to stones or malignancy. Occasionally, it may be required before renal transplant, but routine pretransplant nephrectomy is not favored. This procedure may be complicated by inadvertent adrenalectomy, which would require lifelong steroid replacement.

ESRD in ADPKD patients can be treated with dialysis and transplant. Patients with ESRD from ADPKD do better than patients with ESRD from other causes, and females do better than males. Dialysis is associated with less erythropoietin requirement, better than usual survival and decrease in cyst size, but higher incidence of osteodystrophy, diverticular disease, abdominal pain, hematuria and subarachnoid hemorrhage. Peritoneal dialysis in the patients with PKD may be complicated by peritonitis, infection and hernia.

Renal transplantation is successful in PKD with usual graft survival. Caution should be exercised in performing transplant from a related donor, due to the possibility of PKD in donor kidney. Pretransplant nephrectomy may be required in the presence of recurrent infections, pain, bleeding, stones, neoplasm, inferior vena cava compression and extreme size leading to distressing abdominal symptoms or technical difficulties. Erythrocytosis and complications of diverticulosis are more common in PKD patients after renal transplantation.

Liver cysts are rare in children. The prevalence increases with age to about 75 percent after sixth decade. Of those on renal replacement therapy, 90 percent have liver cysts. They are more common in women, occur at an earlier age in women, and increase with number of pregnancies and estrogen therapy. Hepatic cysts can be detected in half of the patients on CT scan or ultrasound. Enlargement of liver cysts can cause abdominal distension and pain. Liver dysfunction, malnutrition and portal hypertension are unlikely to occur. Percutaneous aspiration and sclerosing therapy (with alcohol or minocycline) can be used to treat solitary cyst. Liver cyst reduction can be done by minimally invasive surgery. Multiple infected cysts may warrant partial liver resection.

Intracranial aneurysms occur in 4 to 10 percent of patients and in 20 percent of those with family history of aneurysms. These may lead to subarachnoid hemorrhage, which is associated with considerable morbidity and mortality. Aneurysms smaller than 7 mm are unlikely to rupture and should be followed conservatively every 1 to 2 year. Larger aneurysms have a risk of rupture up to 2 percent per year and should be intervened with endovascular therapy or surgical clipping. Since the majority of cerebrovascular events in PKD patients are due to hypertension, it should be controlled aggressively.

Routine screening for intracranial aneurysms in asymptomatic individuals is not cost effective. It can lead to psychosocial consequences and difficulty in finding insurance. However, it should be recommended for those who have aneurysmal symptoms (such as bursting headache, transient neurologic symptoms or focal neurological deficits), family history of Berry aneurysm, and those involved in high-risk occupations (such as airline pilot). Imaging methods are likely to be more accurate in the third decade of life. MR angiogram is noninvasive and is more sensitive than ultrasound or CT scan for patients less than 20 years of age.

Pancreatic cysts occur in 10 percent and arachnoid cysts occur in 8 percent of patients with ADPKD.

Novel Therapies

Vasopressin acts on the vasopressin 2 receptor (V2 receptor) to increase cAMP levels, which plays a role in cyst formation. The Vasopressin 2 Receptor (V2 Receptor) antagonists such as Tolvaptan markedly inhibited cyst formation in animal models and seems promising as a future therapy. However, Tolvaptan did not inhibit cyst formation in the liver, which demonstrates that the V2 receptor is absent in the liver. Phase III trials of Tolvaptan are ongoing in the United States. Animal studies have also shown that mTOR inhibitors, such as rapamycin, retard cyst expansion and protect renal function. Small retrospective studies of ADPKD patients after transplantation have shown reduction in the volume of polycystic kidneys in patients treated with rapamycin as compared to patients treated with calcineurin inhibitors. Prospective, randomized trials of rapamycin are underway. There are several other experimental therapies that have shown promise in animal models, but have yet to be studied in human models.

Autosomal Recessive Polycystic Kidney Disease

ARPKD is much rare disorder occurring with a frequency of 1 out of 10,000 to 40,000. The genetic defect on chromosome 6 is transmitted in recessive manner. The parents are not affected and there is variable occurrence in siblings. So, parents of children affected with ARPKD will not have cysts on ultrasound, whereas parents of children with ADPKD will show cysts on ultrasound. ARPKD causes bilateral renal involvement and the cysts develop from collecting ducts. The cysts are small, arranged radially and, unlike ADPKD, there is no intervening normal parenchyma. Due to progressive fibrosis, the kidneys become smaller in size later. ARPKD may be associated with poor development of intrahepatic bile ducts (Caroli's disease) with variable amount of fibrosis.

Clinical Features

ARPKD can present in neonatal period and is associated with a high mortality due to the presence of pulmonary hypoplasia. Survival beyond first month of life predicts more than 75 percent chance of survival beyond 15 years of age. In early childhood presentation, symptoms result from hepatic fibrosis and portal hypertension. Liver cysts are uncommon. The severity of liver involvement is inversely proportional to the degree of renal involvement. Due to early renal failure there is failure to thrive and early onset of hypertension. Presence of abdominal mass, recurrent urinary tract infections and renal osteodystrophy are not uncommon. The disease may also present in early adulthood.

Diagnosis

Ultrasonography is the test of choice, although CT scan and MRI are more sensitive in demonstrating small cysts. By ultrasound, the kidneys are enlarged, smooth and have increased echogenicity. Contrast CT and IVP may show reniform nephrogram with persistence of the contrast in the kidney for more than 24 hours. Prenatal diagnosis can be made by ultrasound after the gestational age of 24 weeks in severe cases.

ARPKD has several differentiating features from ADPKD. Absence of family history, absence of liver cysts and presence of liver dysfunction and portal hypertension with renal involvement help in differentiating ARPKD from ADPKD. Berry aneurysms, aortic aneurysms and Ehlers-Danlos syndrome may be associated with ARPKD.

Treatment

Neonatal presentation of ARPKD with pulmonary hypoplasia has high mortality. Chronic renal failure and liver disease eventually progress in survivors.

Aggressive control of hypertension, prompt treatment of urinary tract infections and avoidance of urologic procedures are recommended. ESRD should be managed in usual manner with dialysis and transplantation. Liver failure is also treated in standard fashion and liver kidney transplantation may be required.

TUBEROUS SCLEROSIS

Tuberous sclerosis (TS) is transmitted as an autosomal dominant disorder with a frequency of approximately 1 in 10,000 individuals. The genetic defect is located on chromosomes 9 and 16, near the gene for ADPKD 1.

Clinical Features

TS is a systemic disorder that can affect skin, brain, bone, liver, lungs, heart and kidney. The classic manifestations of TS are epilepsy, mental retardation and skin abnormalities, especially adenoma sebaceum and ash-leaf spots. Epilepsy usually manifests early in life, but can present later. Cerebral hamartomas, ungual fibromas and angiomyolipoma of lungs may be present.

Angiomyolipomas of kidneys are present in 40 to 50 percent of patients with renal cysts and are considered pathognomonic of TS.

Cystic disease is usually asymptomatic. Hypertension and renal insufficiency are common. Renal failure is the commonest cause of death above 30 years of age in these patients. Retinal hamartoma, cardiac rhabdomyoma and renal cell carcinoma may be present.

Diagnosis

Presence of typical clinical features related to skin, CNS and retinal, family history lead to the diagnosis. The diagnosis can be confirmed by ultrasonography, CT, MRI or angiography.

Treatment

Treatment involves control of epilepsy and management of renal failure in usual manner. Genetic counseling may help in preventing transmission of the disease.

VON HIPPEL LINDAU (VHL) SYNDROME

VHL is an uncommon disorder affecting 1 in 36,000 live births. It is inherited in autosomal dominant fashion with the genetic defect on short arm of chromosome 3.

Clinical Features

VHL usually presents in the third or fourth decade with central nervous system or visual complaints. Renal cysts are common (in up to 76 percent of patients), multiple and irregularly distributed. Renal cell carcinoma can develop in 38 to 55 percent of cases, and is multicentric in up to 60 percent of cases. The cancer develops in fourth or fifth decade and is responsible for 20 to 50 percent of deaths in this group. Cerebellar, spinal and retinal hemangioblastomas are often associated with renal cysts and tumors. Other manifestations include pancreatic cysts and islet cell carcinoma, pheochromocytoma, which may be bilateral, and epididymal masses.

Diagnosis

CT is the diagnostic modality of choice and includes imaging of brain and abdomen. There is no specific treatment for VHL and the complications are treated in usual manner. Family screening and genetic counseling are recommended due to the increased risk of cancer.

Medullary Cystic Disease (MCD)

MCD is a rare disorder transmitted mostly in autosomal recessive (85 percent), but also in autosomal dominant (15 percent) pattern. It can lead to ESRD in young age. It is called renal-retinal dysplasia when accompanied by retinitis pigmentosa, retinal degeneration and pigmentary optic atrophy.

The kidneys are small with small cysts arising from distal and collecting tubules. Pathological examination of the kidney shows about 8 to 10 mm cysts at cortico-medullary junction and in medulla. It is not associated with cysts in other organs or with intracranial aneurysms.

The autosomal recessive form usually presents in young adulthood, and is known as juvenile nephronophthisis. The gene defect is on chromosome 2p. Common symptoms are polydipsia, polyuria and enuresis, probably related to the loss of concentrating ability and renal sodium wasting. The patients are especially prone to prerenal failure. Growth retardation and renal insufficiency occur early. The rate of progression is relatively slow with a doubling time for serum creatinine of about three years. Renal failure usually occurs by the age of 13 years. Anemia is unusually severe and is out of proportion to the degree of renal insufficiency. Renal osteodystrophy is also severe. Due to salt wasting, hypertension is uncommon, or is mild when present. Hematuria is rare. Presence of renal disease at an early age, family history of renal disease, mild hypertension and severe anemia are important clues to the diagnosis of medullary cystic complex.

The autosomal dominant form, known as MCD, presents in early adulthood and causes renal failure by the age of 60 years. The disease may occasionally be associated with hepatic fibrosis, hyperuricemia and gout. Skeletal and CNS defects may be associated. Cysts in other organs or cerebral aneurysms are not seen in this disease.

Diagnosis

Contrast enhanced CT scan demonstrates smooth, normal sized or small kidneys with medullary cysts. IVP may show accumulation of contrast in tubules or may be completely normal. Contrast agents should be used with caution in the presence of renal insufficiency. Ultrasound may not detect cysts in kidneys and renal biopsy may occasionally be necessary to establish diagnosis. Eyes should be checked to exclude retinal abnormality.

Treatment

The treatment of MCD involves maintenance of volume due to the excessive sodium wasting. Dietary sodium intake should not be restricted and sodium supplementation may be required to maintain blood pressure. Renal insufficiency in young patients can retard the growth and needs to be treated. Anemia is treated with erythropoietin. ESRD is managed as usual with dialysis or transplantation. Increased doses of erythropoietin may be required for severe anemia. Osteodystrophy due to secondary hyperparathyroidism may be severe. Related transplant donors should be evaluated very carefully due to the hereditary nature. Genetic counseling with family planning can decrease the frequency of this disease.

Medullary Sponge Kidney (MSK)

MSK is a relatively common disease affecting about 1 in 5,000 to 20,000 individuals in the general population, however, the true frequency may be underestimated. No genetic defect has been identified, but familial cases with autosomal dominant inheritance have been seen. The kidneys are normal in size and have dilated collecting ducts in renal papillae, but the renal cortex is spared.

Clinical Features

The disease affects both sexes and usually presents in fourth or fifth decade. It is bilateral in 75 percent and unilateral in 25 percent of cases. In the absence of complications there are no symptoms and renal function is normal. There may be mild impairment of the ability to concentrate and acidify the urine, resulting in high fractional excretion of sodium, type 1 distal renal tubular acidosis and hypercalciuria. Calcium phosphate stones may form within the dilated collecting ducts. Urinary stones are the presenting symptom in 50 to 60 percent of cases. Hyperparathyroidism may also be associated with this disease. About 20 to 30 percent patients present with recurrent infections of urinary tract and another 10 to 20 percent present with recurrent hematuria. They may be associated with hemi-hypertrophy of the body.

Diagnosis

Intravenous pyelography demonstrates the classic findings of normal to slightly enlarged kidneys, with dilated medullary collecting tubules that are diagnostic. These form a brush-like pattern in renal papillae known as 'bouquets of flowers' or 'paint brush' pattern. These tubules fill with contrast prior to calyceal opacification and then persist, but fail to fill on retrograde pyelogram. Ultrasonography and CT scan help in the diagnosis of stones, abscess or tumors. Calyceal diverticuli, papillary necrosis, renal tuberculosis and other causes of stones should be ruled out with these modalities. Absence of family history, presence of hematuria, urinary tract infections, urinary obstruction, stones, and absence of renal failure differentiate MSK from MCD-complex.

Treatment

The patients with stone formation should be advised to keep a urine output of more than two liters. Thiazide diuretics can decrease hypercalciuria. Urologic intervention may be needed for large or obstructing stones. Renal infections need prolonged antibiotic therapy. Periodic urinalysis, urine culture and renal function tests are recommended to look for crystalluria and infection. The patients should be reassured about the benign nature of the disease.

ACQUIRED CYSTIC KIDNEY DISEASE (ACKD)

Approximately 40 to 100 percent of patients undergoing long-term dialysis develop cysts in kidneys, more in those on hemodialysis than on peritoneal dialysis. Longer duration of dialysis is the key factor to the development of cysts. In those with long-term chronic kidney disease with serum creatinine over 3 mg/dL, 7 to 22 percent of patients develop renal cysts. The cysts can arise from proximal and distal collecting tubules. The cyst fluid is usually clear, but can be hemorrhagic. The cysts can develop in native kidneys as well as in failed transplant kidneys. Male sex, black race and long duration of renal insufficiency seem to be the risk factors for the development of cysts.

Clinical Features

Acquired cysts are usually asymptomatic and may be found incidentally on imaging studies (Fig. 3). The cysts are bilateral, with minimum of five cysts in each kidney required for the diagnosis. Occasionally, the cysts can cause hematuria or retroperitoneal hemorrhage. There may also be a palpable mass, fever or renal colic. Erythrocytosis, hypercalcemia and hypoglycemia have been reported in rare cases. ACKD may be complicated by the occurrence of adenoma or adenocarcinoma, which are more common in a large cyst. There is an increased incidence of renal malignancies (4 to 7 percent over 7 to 10 years) in these patients. Men and those with large cysts resulting in renal enlargement are at higher risk. Matrix-stones, composed of collagenous material may also form.

Diagnosis

Contrast-enhanced CT scan shows bilateral cysts, usually in small kidneys. Small size of kidneys is helpful in differentiating acquired cysts from multiple small cysts. In contrast to ADPKD, there is absence of family history, liver cysts and other systemic manifestations and the kidneys are small. Ultrasonography or MRI can be used when the use of radiocontrast is contraindicated (i.e. advanced renal insufficiency or contrast allergy).

Treatment

Small cysts can occasionally regress after a successful renal transplantation. Supportive measures, such as bed rest and analgesics and supportive treatment are usually sufficient for hematuria and pain, but persistent bleeding can be treated by arteriographic embolization of the kidney.

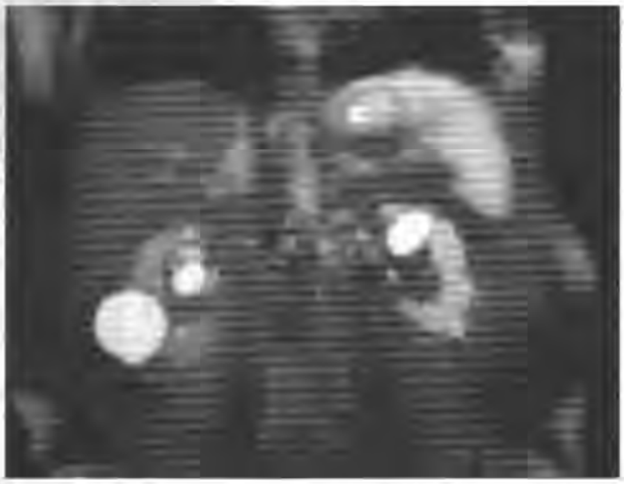

Figure 3: MRI with contrast showing bilateral acquired cystic disease in a patient with advanced diabetic nephropathy

For large cysts, aspiration and cytology can be done to rule out malignancy. Tumors smaller than 3 cm can either be treated with nephrectomy or followed with annual CT scan. Radical nephrectomy is usually performed for large tumors because of the fear of development of malignancy. Any suspicious masses should be removed before a renal transplantation is undertaken.

Screening for ACKD in all dialysis patients is controversial because of a low cost-benefit ratio. Some experts recommend periodic (yearly or every two years) screening after three years of dialysis.

OTHER CYSTIC DISEASES

Cystic renal dysplasia is a defect in renal development. Cystic abnormality can be present in any total or subtotal dysplasia of the kidney. Dysplastic kidneys may sometimes regress in size and rarely neoplasms can develop in a dysplastic kidney. Intravenous urography may not visualize a nonfunctional kidney with total dysplasia and a retrograde pyelogram or CT may be required. Resection of a dysplastic kidney may be required if it is responsible for hematuria, infection or hypertension.

Solitary multilocular cysts are rare, unilateral, and are large. They present early in males and late in females. These may need surgical excision if causing obstruction. Partial nephrectomy may be required if there is a suspicion of malignancy.

Pyelocalyceal cysts arise from minor or major calyx. These are unilateral and rarely may be complicated by recurrent infection or development of stones.

Renal lymphangiomatosis is the dilatation of renal lymphatics. Stones may form in 10 to 40 percent. These remain asymptomatic unless complicated by recurrent infection, obstruction, renal ischemia and hypertension. CT or ultrasonography is helpful in diagnosis.

Hilar cysts are pseudocysts that result from atrophy of fat in the renal hilum in debilitated patients.

Perinephric pseudocysts contain urine that leaks from ruptured renal cyst. The diagnosis can be made with the help of CT scan. If causing obstruction, this may require surgery including nephrectomy.

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Acute and Chronic Urinary Tract Obstruction in Adults: Pathophysiology, Diagnosis and Management

Anil K Mandal

INTRODUCTION

Before discussing the etiology, pathophysiology and the clinical presentation of urinary tract (UT) obstruction, it is important for the readers to have some fundamental knowledge of the anatomy of urinary tract. A thorough knowledge of the anatomy of UT will facilitate the readers to determine not only the cause for obstruction but also the location of the obstruction. The latter is immensely important for developing therapeutic strategy and determining implication of the obstructive effect on overall renal function in the long haul. The cause as well as the location of UT obstruction differ widely between male and female genders, hence an effect of obstruction on nephron function and long-term prognosis will also vary between male and female genders.

ANATOMY OF THE URINARY TRACT

Urinary tract consists of kidneys, ureters, bladder and urethra. The kidneys, one on each side, lie perpendicularly along the vertebral axis extending from thoracic vertebra 12 (T12) to lumbar vertebra 3 (L3). The ureter runs inferiorly from each kidney in close relation to aorta and inferior vena cava and passes over the pelvic brim at the bifurcation of the common iliac artery. It runs along the lateral wall of the pelvis and then enters the urinary bladder. The funnel-shaped renal pelvis is continuous inferiorly with the ureter. The word pelvis is derived from the Greek word pyelos, meaning a basin (or container), where urine from the kidney first collects. Within the renal sinus, the renal pelvis usually divides into two wide, cup-shaped major calices. Each major calyx is subdivided into 7-14 minor calices. The urine empties into a minor calyx from collecting tubules that pierce the tip of a renal papilla obliquely. The urine then passes through the minor calyx, pelvis, and ureter to enter the urinary bladder. There are 7-14 renal papillae in each kidney. These papillae are subject to damage by infection, ischemia or analgesics.

The urinary bladder is a hollow muscular organ and located anterior to the uterus and vagina in the female. The anatomy of the urethra also differs markedly between male and female. The female urethra is about 4 cm long and runs obliquely down and forward from the bladder. On the other hand, the male urethra has a long tortuous course. It is 20 cm long and has several segments. The first segment is completely surrounded by the prostate gland (called prostatic urethra). From the prostatic urethra, urine passes into a short segment called membranous urethra and then into the covernous urethra located in the penis.

Relationship of Anatomy of Urinary Tract to Clinical Manifestations of Urinary Tract Obstruction and Related Conditions

Each kidney, invested by a fibrous renal capsule, is embedded in a substantial mass of perirenal fat that constitutes a fatty renal capsule. The fatty renal capsule is in turn covered by fibroareolar tissue called the renal fascia. This fascia encloses the kidneys and the adrenal glands and helps to maintain these organs in position.

Thus, blood from an injured kidney or pus from a perinephric abscess may force its way inferiorly into the pelvis and between anterior and posterior layers of pelvic fascia.[1]

The close relationship of the kidneys to psoas muscles explains acute or chronic back pain from acute swelling or progressive enlargement of the size of the kidneys. This relationship also accounts for increase of pain upon extension of thighs during inflammation in the pararenal regions.[2]

Rapid excessive distension of the ureter causes severe rhythmic pain called ureteric colic. Distension of the ureter may occur from occlusion of the lumen of the ureter by a stone, a blood clot, necrotic papillae, purulent materials or even a large volume of urine passing through the ureters at a very rapid rate. Ureteric colic is a sharp, stabbing pain that follows the course of the ureter (from loin to the inguinal region or groin) as the solid material such as a stone or a blood clot moves down the ureter. In men the pain is frequently also referred to the scrotum, and in women, it may radiate to the labia majora. The ureter is supplied with pain afferents that are included in the lowest splanchnic nerve; the impulses enter via T12 and L1 segments. This explains why the colic is referred to the lateral and inguinal regions of the abdomen.[1]

Large renal calculi, such as staghorn calculi are unable to enter the ureter, hence remain in the kidney or renal pelvis. In this location, stones may cause bleeding, infection, obstruction to the passage of urine and loss of kidney function.[1] However, renal colic is uncommon is staghorn calculi.

URINARY TRACT OBSTRUCTION

Obstruction can occur anywhere in the UT and may develop in an acute or chronic fashion. Obstruction can occur in the lower urinary tract consisting of bladder and urethra or in the upper urinary tract comprising kidney, pelvis or ureter. Obstruction of the upper UT can be unilateral or bilateral, and partial or complete. Similarly lower urinary tract obstruction can be partial or complete.

The causes and sites of UT obstruction differ widely between adult males and females. However, UT obstruction is much more common in males than females. Also lower UT obstruction is by far the most common type of chronic urinary tract obstruction in males.

Causes and Sites of Obstruction

Lower Urinary Tract and Chronic Urinary Obstruction

1. Lower urinary tract obstruction caused by an enlarged prostate is the number one cause of chronic urinary obstruction in males.
2. Lower urinary tract obstruction due to stricture of urethra caused by gonorrhea used to be a very common cause of urinary obstruction in the past. Stricture of urethra is more common in males than females. However, rapid detection and adequate treatment of gonorrhea as well as extensive sex education by Public Health Administration have resulted in a decline in the incidence of gonorrhea, and consequently stricture of urethra.
3. Tumor of the bladder encroaching upon the bladder outlet is an uncommon cause of chronic lower urinary tract obstruction.
4. Compression of the bladder due to gravid uterus or large uterine fibroid is a common cause of reversible lower UT obstruction among the females.

Unremitting lower UT obstruction results in progressive distension of the ureter and pelvis bilaterally as well as loss of nephron function. The overall clinical outcome from this anatomic obstruction is chronic renal failure.

Upper Urinary Tract Obstruction and Acute or Chronic Urinary Obstruction

Upper urinary tract obstruction is commonly unilateral and transient. A renal stone is the most common cause for unilateral ureteral obstruction. Other causes of unilateral ureteral obstruction include intrinsic occlusion by a tumor, blood clots, necrotic papillae or extrinsic compression by a tumor (lymphoma, metastasis), hematoma or aberrant renal artery. Unilateral ureteral obstruction may occur from strictures. Strictures are bands of fibrous tissue that narrow the lumen of ureter and can be caused by infections, injury, or drugs such as methysergide. Strictures may develop from congenital abnormalities.[2] Unilateral ureteral obstruction will result in decrease of nephron function in the affected kidney, but does not give rise to renal failure unless the contralateral kidney has decreased functional reserve.

However, ureteral obstruction induced by any one of the causes as stated above in a solitary kidney including a transplanted kidney will result in renal failure.

Bilateral ureteral obstruction is uncommon, but can occur as a result of retroperitoneal fibrosis or precipitation of uric acid or sulfonamide crystals. A common cause of bilateral ureteral obstruction in females is metastatic spread of cancer of cervix to the parametrium. Retroperitoneal fibrosis can occur as a result of carcinoma, drug (methysergide) or without any identifiable cause (idiopathic). It is very uncommon nowadays to find patients with acute bilateral ureteral obstruction caused by precipitation of uric acid crystals in tumor lysis syndrome or sulfonamide crystals from use of nonabsorbable sulfa drugs as did in the past.

Patient's Illustrations

The following two patients will exemplify reversible or irreversible renal failure caused by chronic lower urinary tract obstruction.

Patient Number 1

AT, a 60-year-old black male was admitted to a local hospital, Dayton, Ohio on August 30, 1993 with the following complaints for one month.

1. Difficulty in passing urine.
2. Feeling of incomplete emptying of bladder
3. Nocturnal frequency

Physical examination: Most significant finding was suprapubic fullness and dullness (Distended Bladder).

Renal function rapidly deteriorated from July 1993. This is accompanied by a decrease in hematocrit. The evidence is presented in Table 1.

Decompression of bladder by an indwelling catheter had resulted in restoration of renal function and electrolytes to normal or near normal levels (Table 1). Ultrasound of kidneys two days after bladder evacuation showed slight pelvicalyceal dilatation. It should be noted that hyperkalemia out of proportion to the degree of azotemia as in this patient is suggestive of UT obstruction. He underwent transurethral resection of prostate in later part of September 1993. Follow -up after six months showed normal renal function and electrolyte values BUN 14 mg/dl, serum creatinine 1.1 mg/dl, Na^+ 140 mEQ/L K^+4 mEQ/L, CO_2 24 mEq/L, Cl 103 mEq/L. His hematocrit progressively increased to 44.5 percent on December, 1994.

Patient Number 2

CA, an 80-year-old white male was admitted to a local hospital, Dayton, Ohio on July 7, 1993 with the following complaints:

1. Loss of appetite
2. Weight loss of 30 lbs. in 6 months
3. Intermittent gross hematuria for two years

Physical examination: Cachetic appearance, diffusely enlarged prostate. Otherwise unremarkable.

Table 1. Serial laboratory studies

Date	*BUN (mg/dl)*	*Serum creatinine (mg/dl)*	*NA^+ (mEq/L)*	*Cl^- (mEq/L)*	*K^+ (mEq/L)*	*CO_2 (mEq/L)*	*Hematocrit (%)*
May 15, 1992	18	1.1	142	104	4.1	28	
July 8, 1993	13	1.1	139	103	4.9	28	43
Aug. 27, 1993	37	3.5	146	114	6.2	17	
Aug. 20, 1993	—	—	—	—	—	—	35.3
Aug. 30, 1993	48	7.2	140	111	6.5	16	
Foley Catheter was inserted in bladder + Kayexalate suspended in Sorbitol PO ordered.							
Aug. 31, 1993	27	3.2	145	115	5.6	16	
Sept. 2, 1993	—	—	—	—	—	—	34.4
Sept. 6, 1993	17	1.9					
Sept. 8, 1993	17	1.5	135	100	5.4	23	32.7

PO = per oral 40 ml initial dose followed by 20 ml every 6 hours for 24 hours

Admission Laboratory Studies	
Glucose	120 mg/dl
BUN	112 mg/dl
Serum creatinine	12 mg/dl
Na$^+$	141 mEq/L
K$^+$	6.7 mEq/L
Cl$^-$	113 mEq/L
Total CO_2	8 mEq/L
Calcium	10.3 mg/dl
Phosphate	7.4 mg/dl
Uric acid	10.1 mg/dl

THERAPY

1. Intravenous infusion of saline with 2 ampules of sodium bicarbonate per liter bag was administered at the rate of 150-200 ml/hr.
2. Kayexalate suspended in sorbitol (5 gm in 20 ml) was given in a dose of 20 ml three times daily.

Ultrasound of the kidneys (July 8, 1993): Bilateral hydronephrosis, and a large bladder mass were found.

Cytoscopy (July 9, 1993): A large mass occupying more than half of the bladder volume was found. Biopsy of the mass showed poorly differentiated bladder cancer. A retrograde pyelogram showed global dilatation of the left kidney and hydroureter. Right kidney pelvicalyceal system was less severely dilated as was the ureter.

Bilateral nephrostomy tube was placed on July 9, 1993. The functional status of each kidney was assessed by collection of nephrostomy drainage and detailed analysis of the drainage (Table 2). Right nephrostomy produced good volume of urine, while left nephrostomy had small volume (15-30 ml/day).

Table 2. Nephrostomy drainage analysis

	Right nephrostomy drainage	
July 1993	17	21
Volume	4100	1400
Na$^+$ (mEq/L)	370	ND
Cl (mEq/L)	341	ND
K$^+$ (mEq/L)	72	ND
Creatinine (g)	0.8	0.5
Ccr (ml/min)	11.8	10

Ccr = creatinine clearance
ND = not done

Nephrostomy drainage analysis showed slight or no function of the left kidney, but some remaining functions of the right kidney. The findings of retrograde pyelogram were consistent with the drainage analysis. Although overall nephron function of the right kidney was markedly reduced, good recovery of overall renal function was evident (Table 3). BUN and serum creatinine progressively decreased to 33 mg/dl and 2.9 mg/dl, respectively and serum electrolytes returned to near normal levels (Table 3).

Ultrasound of kidneys repeated on July 20 (11 days after nephrostomy drainage) showed complete resolution of hydronephrosis in the right kidney.

PATHOPHYSIOLOGY

These two patients illustrate that the severity of "nephron loss" and the degree of "irreversibility of overall renal function" depend largely on the estimated duration of obstruction and the extent of obstruction. For instance, in patient number 1, renal function reversed completely to normal level (as determined by BUN and serum creatinine) upon decompression of bladder by an in situ bladder catheter, whereas in patient number 2, left kidney was completely non-functioning, and the right kidney

Table 3. Serial laboratory studies

1993, July	*7*	*8*	*9*	*17*	*25*	*30*
Na$^+$(mEq/L)	141	137	131	137	135	130
K$^+$(mEq/L)	6.7	5.3	3.6	4.1	5.7	4.8
Cl(mEq/L)	113	110	98	102	98	92
BUN(mg/dl)	112	106	90	41	24	33
Creatinine (mg/dl)	12	11.8	9.8	4.7	2.7	2.9
CO_2 (mEq/L)	8	11	18	25	26	29

was functioning only slightly. The fundamental differences between these two patients are the duration and extent of obstruction. From history, it is quite apparent that patient number 1 had partial obstruction of the bladder outlet by an enlarged prostate of a relatively short duration, whereas patient number 2 obviously had almost total bladder outlet obstruction by an enlarging tumor of 2 years or more.

Lower urinary tract obstruction is seldom complete; therefore hardly gives rise to complete cessation of urine flow or anuria. Bladder outlet or urethral obstruction subjects the bladder to high hydrostatic pressure; as a result, bladder first undergoes hypertrophy to overcome the obstruction, and partially empty the bladder. Therefore, otherwise normal individuals may not always develop palpably distended bladder, whereas disabled or chronically ill subjects such as diabetics who are unable to partially empty the bladder or don't feel distension as a result of autonomic neuropathy are frequently brought into emergency room with highly distended urinary bladder. Their main complaint may be pain and discomfort of lower abdomen. Hypertrophy of the bladder musculature causes occlusion of the intravesicular ureteral segment, with relative obstruction of the ureterovesical junction and increased back pressure on the ureters and kidneys resulting in dilatation of ureters and hydronephrosis. In the presence of bladder outlet obstruction, the intravesical pressure increases markedly during micturition. This high pressure is transmitted to the kidneys in the form of reflux of urine during voiding. Even in the absence of reflux, pressure in the bladder during the storage phase is important for the outcome of lower urinary tract obstruction. In case of high pressure chronic bladder retention in which intravesical pressure is higher than the intra-abdominal pressure, upper urinary tract will likely to deteriorate.[3,4]

The pathophysiology of upper urinary tract obstruction is far more complex than that of lower urinary tract. Complete obstruction of both ureters or of a single ureter in a single functioning kidney such as transplanted kidney results in anuria. Obstruction of a ureter causes dramatic changes in peristaltic activity and intraluminal pressure of the pelvis and ureter. Peristaltic contractions occur at a frequency of two to six per minute to propel urine from the kidney to the bladder. The resting ureteral pressure is < 5 mmHg and reaches 20 to 40 mmHg with peristaltic activity.[3] The earliest change of an ureteral obstruction is an increase in hydrostatic pressure proximal to the obstruction. The extent of the increase in hydrostatic pressure also depends on the urine flow at the onset of obstruction and the degree of obstruction. This explains why partial ureteral obstruction may remain asymptomatic as long as the urine flow is low. Low urine flow minimizes backflow of urine. Due to backflow of urine proximal to obstruction and increased hydrostatic pressure, the ureteral wall tension increases up to a point when the ureteral walls fail to respond to peristalsis and become progressively weak. The elevation of hydrostatic pressure causes both the diameter and length of ureter to increase. The collecting system becomes dilated, and if production of urine remains high collecting system continues to dilate.

The elevated ureteral pressure is transmitted to the tubules and to the Bowman's space resulting in decrease of glomerular filtration rate (GFR). Although renal blood flow is normal or high, GFR remains low.

A number of vasoconstrictor and vasodilator substances including angiotensin II, thromboxane B and prostaglandins (PGs) may have interactive roles in the pathophysiologic changes stated above. The precise interactive role of any of these mediators is difficult to ascertain. However, prostaglandin E_2 (PGE_2) may have an influence on postobstructive diuresis.

As the pelvicalyceal dilatation continues or is sustained, progressive nephron loss ensues. Renal clearance and tubular function decrease. Tubular function abnormalities characterized by concentration and acidification defects may become evident long before decreased GFR causes retention of BUN and serum creatinine. The concentration defect is manifested by polyuria and nocturia, dehydration and further worsening of renal function. The acidification defect may result in persistently alkaline urine, a cause for recurrent urinary tract infection. Severe metabolic acidosis, and hyperkalemia, which are out of proportion to azotemia are common presenting features of patients with chronic UT obstruction (or obstructive uropathy).

DIAGNOSIS

The diagnosis of urinary tract obstruction, whether it is upper or lower, acute or chronic, can be defined by a good history, a complete physical examination and routine laboratory studies. Radiological studies determine the cause and site of obstruction. The history and the physical examination in patient number 1 are typical for lower urinary tract obstruction caused by a prostatic enlargement. On the other hand, the history of intermittent gross hematuria for 2 years and severe loss of weight in patient number 2 suggest UT malignancy. The routine laboratory studies in both patients showed severe hyperkalemia. Hyperkalemia was clearly out of proportion to the degree of azotemia in patient number 1 but not necessarily so in patient number 2. Patient number 2, however, had severe metabolic acidosis with serum CO_2 (HCO_3) of 8 mEq/L upon admission. Therefore, the history, physical examination and routine laboratory studies were suggestive of urinary tract obstruction in both patients.

The first radiological study is ultrasound of kidneys and bladder. Ultrasound (or sonogram) is a non-invasive and sensitive technique and recommended in every patient with acute or chronic renal failure who is a suspect of urinary tract obstruction. However, acute UT obstruction can occur with minimal pelvicalyceal dilatation, and hence ultrasound findings can be interpreted as normal. This is more common in the first 24 to 48 hours of acute obstruction. However, if pelvicalyceal dilatation is noted and the history is suggestive of lower urinary tract obstruction, as in the patients illustrated, cystoscopy and retrograde pyelogram is the next procedure of choice. This procedure allows inspection of urethra as well as bladder and to perform biopsy of a lesion, if any found. Retrograde pyelogram demonstrates anatomy of ureter, renal pelvis and site and type of ureteral obstruction. In case of unilateral or bilateral ureteral obstruction for example by stones, intravenous pyelogram (IVP) is the procedure of choice. Although IVP carries a definite risk on the renal function, yet it is more rewarding than ultrasound or CT scan when stone is a consideration.

If a lower obstruction is detected and a urologic intervention is contemplated, it is essential to know the overall renal function and the intergrity of the upper urinary tract. The overall renal function is grossly assessed by a basic metabolic panel, which provides BUN, serum creatinine and electrolytes. An estimate of the GFR can be obtained by a creatinine clearance with collection of 24 hours urine for volume and creatinine and a midpoint blood sampling for serum creatinine. Creatinine clearance is calculated using the standard formula UV/P, where U = urine creatinine in mg/dl, V = Volume of urine in ml/min (24 hours = 1440 minutes) and P = plasma (serum) creatinine in mg/dl.

The anatomy of upper urinary tract can be evaluated by excretory pyelography or diuresis renography. In patients with decreased renal function diuresis renography will be safer than excretory urography, since the latter may cause further deterioration of renal function from the use of contrast.

DIURESIS RENOGRAPHY (OR DIURETIC RADIONUCLIDE UROGRAPHY)

Diuretic radionuclide urography is a useful test to measure renal function and determine if physiologically significant obstruction is present. This test is particularly useful if previously recognized nephroureteral dilatation represents significant obstruction. It is important to know that ureteral and pelvicalyceal dilatation do not necessarily indicate lower tract obstruction, as this feature can be due to reflux of urine without definable lower urinary tract obstruction. This procedure is done by intravenous injection of a radionuclide (Tc-99mDTPA and MAG3), followed by an IV bolus of furosemide in a dose of 0.3 to 0.5 mg/kg. Renal and bladder imaging are done using a gamma scintillation camera, and data are obtained in a computer.

Three types of patterns can be found. These are normal; dilated, non-obstructive pattern (as in reflux) or obstructive pattern. When dilated, non-obstructive pattern is found then the next procedure is *voiding cystourethrogram.* Voiding cystourethrogram is done to confirm reflux as a cause of dilatation of the collecting system than to diagnose upper urinary tract obstruction. In cases where lower tract obstruction is secondary to a stricture of urethra or enlargement of the prostate causing stretching of the urethra, inserting a catheter into the bladder may be most difficult. The urethra may then be evaluated through a retrograde urethrogram or injecting contrast through suprapubic bladder puncture.

In case of malignancy *computerized axial tomography (CT) Scan* is recommended to determine the site of obstruction and aid cancer staging.

Management and Prognosis

1. Medical (or conservative)
2. Urologic (surgical)
3. Dialysis

Medical management is advocated mainly to treat fluid, electrolyte abnormalities and metabolic acidosis as it is presented in patients number 1 and 2. If a patient is symptomatic of uremia, and ultrasound of kidneys shows bilateral hydronephrosis, symptoms can be promptly relieved by unilateral or bilateral nephrostomy drainage (exemplified in patient number 2). In cases of obstruction caused by advanced malignancies, a bilateral nephrostomy is all that should be done.

Where the symptoms are mainly attributed to lower urinary tract obstruction and ultrasound shows mild obstructive features, as in patient number 1, decompression of bladder by an indwelling catheter should be done to relieve symptoms. If renal function is markedly impaired, time should be allowed for renal function to improve and symptoms to abate. Once these are accomplished, investigations should be undertaken to determine the cause and site of obstruction. For example, a renal stone obstructing one or both ureters may pass. If stones are not passed, ureterostomy may have to be done to remove the stone. Similarly for enlarged prostate causing bladder outlet obstruction transurethral resection of prostate (TURP) is usually recommended. However, prior to TURP, a course of alpha blocker, doxazosin (Cardura)* or terazosin (Hytrin)* should be tried for several weeks. Cardura is better tolerated than hytrin. Cardura causes least postural hypotension and dizziness. It is usual to start cardura 1-2 mg at bed time daily and gradually increase to 4 to 6 mg at bedtime daily. Nocturia decreases in number with regression of size of prostate. Residual volume decreases, retrograde flow of urine diminishes and pelvicalyceal dilatation is regressed. Consequently GFR increases. These agents inhibit smooth muscle proliferation of the prostate, and by reducing the size of the prostate, relieve bladder outlet obstruction. In case of acute renal failure associated with uric acid stone and hyperuricemia treatment with intravenous saline with added sodium bicarbonate in the bag will enhance uric acid excretion. Allopurinol 300 mg daily if renal function is normal should be prescribed to inhibit uric acid production. If no cause of obstruction is found and there is no evidence of malignancy in a patient with bilateral hydronephrosis and chronic renal failure, hemodialysis is the recommended treatment. Renal transplantation also can be considered.

After relief of bladder outlet or bilateral ureteral obstruction in the uremic patient, postobstructive diuresis may ensue. This syndrome is characterized by a urine flow which may be as high as 5 to 10 percent of the filtered volume (10-20 liters of urine in 24 h) and as much as 20 percent of the filtered sodium. The exact mechanism of post-obstructive diuresis is not fully known. However, impaired urine concentrating ability (nephrogenic diabetes insipidus) and the osmotic diuresis caused by retained urea have been considered. Excessive PGE_2 production giving rise to natriuresis and diuresis has been postulated. *Postobstructive diuresis* should be treated by adequate replacement of fluid and electrolytes in the form of normal saline with addition of small amount of potassium (20 mEq/L bag of normal saline). This excessive diuresis may last for several days, but fluid replacement should be cut back slowly to promote tubular reabsorption of water. To promote water reabsorption by the collecting tubules, dDAVP (desmopressin) 1 to 2 mcg (ug) subcutaneously twice daily may be used. Due to possible role of PGE_2 in this postobstructive diuresis, small dose of indomethacin may be tried.

Urologic procedure can be immediate or elective. Immediate urologic intervention consists of unilateral or bilateral nephrostomy, suprapubic cystostomy or intraureteral stent placement. While nephrostomy or stent placement is usually done by an interventional radiologist, suprapubic cystostomy is done by a urologist. These procedures are done to relieve symptoms mainly due to azotemia and allow stabilization of the patient's general condition. In case of UT obstruction due to malignancy such as cervical cancer in females or bladder cancer with limited survival, these surgical procedures are desirable as they offer reasonable quality of life. Survival may not be prolonged. *Maintenance hemodialysis* is considered when chance of recovery of renal function is negligible even after relief of obstruction, or in case no cause is found for hydronephrosis. In case of ureteral obstruction, a stent can be placed even when renal function is grossly impaired. If a surgery is planned and the patient has significant renal function impairment, hemodialysis is recommended preoperatively to control azotemia, correct fluid and electrolyte abnormalities and minimize the risk of excessive bleeding. In short of hemodialysis, a surgical procedure can be undertaken in a uremic patient with a reasonable safety, provided dDAVP (desmopressin) is administered (0.3 to 0.5 mcg/kg in 50 ml normal saline infused in 30 minutes) one hour before surgery and immediately following surgery. Surgery should ideally be planned between 8 and 24 hours after a hemodialysis treatment. This will minimize the risk of heparin-induced hemorrhage. Similarly, the next hemodialysis treatment may be postponed for one to two days following surgery.

PROGNOSIS

Notwithstanding advancement of knowledge in the understanding of pathophysiology and management of urinary tract obstruction, there is yet much to be learned to determine degree of recovery of overall renal function after relief of sustained lower urinary tract or bilateral ureteral obstruction. Recurrent unilateral ureteral obstruction although may compromise function of the affected kidney temporarily, overall renal function is not affected. The contralateral kidney undergoes compensatory hypertrophy, develops hyperfiltration and makes up the loss from the affected kidney. The situation is quite different in case of obstruction of bilateral ureteral, of solitary kidney or of lower urinary tract. In these situations, there is no compensation and consequently renal function may deteriorate irreversibly if the obstruction is unremitted.

A very important question is often asked, whether renal function will recover fully or partially after relief of sustained obstruction for an unknown period of time. The two patients illustrated here should provide a reasonable answer to the question asked. Obviously, if the obstruction is of short duration, restoration of renal function to normal or near normal level upon relief of obstruction is a reasonable expectation. On the other hand, if obstruction is of long duration (months to years), the chance of return of reasonable amount of renal function upon relief of obstruction is small. However, any prediction should be made with caution. This is exemplified in patient number 2. In this patient right kidney had some residual function left. Recovery of renal function might have been better if his bladder outlet obstruction due to tumor had been relieved. Therefore, the lesson learned from these illustrations is that we should make all efforts to relieve obstruction with a hope to help restore renal function sufficiently, hence allowing patients to live without renal replacement therapy.

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Pathogenesis and Management of Bleeding Disorders in Renal Failure

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INTRODUCTION

The association between increased bleeding tendency and renal failure has been recognized for centuries and has become the subject of much investigation. Morgagni in 1764 described bleeding as the main clinical feature in a patient with renal insufficiency. In the early 1800s Bright reiterated this relationship, noting that patients with renal failure often presented with purpura. In the predialysis era, bleeding was a major and frequent manifestation of renal failure. Hemorrhage was often severe and difficult to control; in fact, bleeding was a major cause of death in these patients. Since the introduction of dialysis, the incidence of severe bleeding has decreased significantly, but bleeding remains a serious problem in some patients. A minor hemorrhagic diathesis is common in uremia and is an important cause of morbidity. In uremic patients who may require an invasive procedure (such as placement of nephrostomy tubes or creation of arteriovenous fistula for dialysis), this increased bleeding tendency may constitute a threat. Therefore before performing any such procedure, the potential for bleeding must be evaluated and management plans kept ready to minimize bleeding.

TYPES OF BLEEDING MANIFESTATIONS

The hemostatic defect in uremia is one of primary hemostases (to be discussed later) and gives rise to bleeding mainly from the mucous membranes. The common bleeding sites are nasal (epistaxis), uterine (menorrhagia), gastrointestinal and gingival. In addition, increased bleeding from venipuncture sites, easy bruising and ecchymosis are also common.

Gastrointestinal Bleeding

Gastrointestinal (GI) bleeding is a frequent complication of acute or chronic renal failure and a cause for hospital admission. Spontaneous GI bleeding is rare. The vast majority of patients have an underlying pathologic lesion, most commonly a peptic ulcer disease. Other GI lesions are diverticulosis and cancer of the colon. An obscure cause of GI bleeding in renal failure patients is angiodysplasia. Angiodysplasia is most commonly found in the right colon, however for unknown reasons uremic patients have a predilection for angiodysplastic lesions involving the stomach or duodenum.

Subdural Hematoma

Subdural hematoma is a form of spontaneous hemorrhage occurring in 2 to 6 percent of hemodialysis patients. Patients who are hypertensive or suffer head trauma are at the greatest risk for development of subdural hemorrhage. Even a trivial head trauma can be sufficient to produce subdural hematoma. Mortality is high, approximating 90 percent in those patients requiring emergency surgical evacuation of the intracranial hemorrhage.

Spontaneous Subcapsular Hematoma

Spontaneous subcapsular hematoma of the liver is a well-recognized complication in uremia and thought to represent the second most common form of spontaneous hemorrhage in this population. Patients typically present with right upper quadrant pain, fever and sometimes elevated bilirubin and alkaline phosphatase levels. The hematocrit may fall depending on the extent of the subcapsular hemorrhage.

Spontaneous Retroperitoneal Hemorrhage

Spontaneous retroperitoneal hemorrhage is rare in uremic patients. Retroperitoneal hemorrhage in uremic patients may occur as an iatrogenic complication of percutaneous femoral catheterization for hemodialysis or ruptured cysts in acquired cystic disease of the kidney. Clinical manifestations include acute onset of abdominal, flank or back pain, abdominal distension and decrease in hematocrit. Abdominal ultrasound or CT scan can confirm the diagnosis.

Hemorrhagic Pericarditis

Hemorrhagic pericarditis was common and occasionally fatal in the days before dialysis. Nowadays it is a rare site of spontaneous hemorrhage in uremics.

PATHOPHYSIOLOGY

The hemostatic system typically is divided into three components:

1. Primary hemostasis
2. Secondary hemostasis
3. Fibrinolysis

Primary Hemostasis

a. Platelet-vessel interaction = Platelet plug
b. Platelet-platelet interaction

Secondary Hemostasis

a. Plasma coagulation factors
b. Generation of the fibrin clot

Fibrinolysis = Clot Lysis

The blood vessels are lined by a continuous monolayer of endothelial cells that function, in part, as a nonthrombogenic surface. Disruption of, or injury to, the endothelial surface results in exposure of the blood components to the subendothelium. The subendothelium contains a variety of substances (collagen, tissue factor, negatively charged surfaces, etc.) that promote the formation of both the platelet plug and the fi
clot. Platelets adhere to the exposed subendoth
structures, including collagen as well as other yet po
defined insoluble components. Plasma von Willebr
factor (vWf) is necessary for adherence of the plat
to the subendothelium and acts as an anchor betw
these two structures.

A patient is presented here to exemplify the defe
primary hemostasis as a cause of bleeding in renal fail

56-year-old African-American male, develo
diabetic end-stage renal disease, and had cirrhosis of
with moderate to massive ascites and congestive h
failure. He was treated with insulin, digoxin, furose
(Lasix®), and multivitamins. He was transferre
a local hospital in Dayton, Ohio for the purpos
hemodialysis. In the emergency room of the hospital
had large melena and his blood pressure dropped.
was diaphoretic, and ecchymoses were noted over
extremities. He had bilateral below knee amputat
Rectal examination showed gross melena.

Laboratory

Hematocrit/hemoglobin	12.6%/4.0 g/dl	**One wee prior 28%/8.9**
Platelet count	1,77,000/cmm	
PT	10.5 sec (N = 10-13)	
PTT	31 sec (N = 27-35)	
Serum creatinine	8.3 mg/dl	
Serum urea nitrogen (BUN)	85 mg/dl	
Bleeding time	>15 min (N = 3.5-9.5)	

Patient was admitted to the medical inten
care unit and treated with packed cell transfus
fresh frozen plasma and hemodialysis. GI blee
continued and his condition became very unstabl
received multiple transfusions of packed cells, f
frozen plasma, intravenous desmopressin and
hemodialysis. Three days later, his hematocrit incre
to base line of 28 percent with arrest of GI blee
Gastrointestinal endoscopy was done and found to
multiple gastroduodenal ulcerations. He was place
ranitidine (Zantac®) orally. He remained on mainten
hemodialysis, but died six months later. However, he
no recurrence of GI bleeding.

RELEVANT QUESTIONS THAT MAY BE ASKED IN UREMIC BLEEDING

1. What are the identifiable factors that contribute to the prolonged bleeding time?
2. Does the prolonged bleeding time alone cause bleeding in renal failure patients or it does so in the presence of associated lesion(s)?
3. What are the appropriate therapeutic modalities to control uremic bleeding?

Prolonged Bleeding Time

Prolonged bleeding time (BT) is the consistent laboratory abnormality in severe renal failure (uremic) patients. Bleeding time is the most useful clinical laboratory test to assess both bleeding risk and response to therapy. It correlates better with clinical bleeding complications than indices of azotemia or *in vitro* platelet aggregation tests. Bleeding time was determined in 31 patients with variable degrees of chronic renal failure. BT was within normal range in the majority of the patients. Except in one patient each, mean BT was not significantly longer than the control in mild and moderate chronic renal failure patients. In severe chronic renal failure, mean BT (7.31) was significantly ($P < .005$) longer than the control mean BT (4.79 min). Although BT is almost invariably prolonged in severe azotemia, no direct correlation has been obtained between BT and the severity of azotemia.

The abnormal BT in uremic patients is an overall marker of the defect in primary hemostasis, and platelet adherence to foreign surfaces.

Factors that Affect Bleeding Time

The factors that may influence BT are anemia, von Willebrand factor, platelet-platelet interaction, parathyroid hormone, thromboxane and prostaglandins, and nitric oxide (NO) activity.

Anemia

The low hematocrit seems to be the most important factor associated with a prolonged BT and probably plays a major role in the pathogenesis of uremic bleeding. A highly significant negative correlation was found between BT and packed cell volume (PCV) ($r = 0.55$; P less than .001). The prolonged BT in uremic patients may be shortened by elevation of hematocrit with packed red cells transfusion, and/or by recombinant human erythropoietin (r-HuEPO) therapy.

Packed cell transfusion also improves platelet adhesiveness. The effects of correction of anemia with r-HuEPO were examined on the hemostatic defects in uremia. Anemia improved significantly 12 weeks after r-HuEPO therapy (stage II) compared to pretreatment level (stage I) and 6 weeks discontinuation periods (stage III). BT significantly shortened at stage II and again prolonged in stage III. BT exceeding 20 min was observed in almost 50 percent patients before r-HuEPO therapy. BT decreased to less than 20 min in 50 percent patients during the treatment period.

Anemia is not, however, the sole cause of abnormal BT and the bleeding manifestations in uremia. In anemic patients without uremia, BT still correlated negatively with PCV, but for any one PCV level BT was significantly shorter in nonuremic than in uremic patients. Moreover, platelet adhesion in normal blood with an artificially reduced hematocrit was significantly higher than that in uremic blood at corresponding PCVs. Finally, although erythropoietin substantially corrects BT in most uremic patients, BT still remains prolonged. Thus, factors other than anemia operate in uremia to prolong BT and reduce platelet adhesiveness.

von Willebrand Factor (vWf)

vWf plays a crucial part in primary hemostasis because it induces platelet adhesion and aggregation through specific glycoprotein receptors. Published reports demonstrate vWf abnormalities in uremia. The data is somewhat conflicting about the type of abnormalities. However, reduction or absence of the largest plasma vWf multimer was noted uremic patients. The platelet Von Willebrand contents was significantly decreased. These defects may play a role in the prolonged bleeding time and the clinical bleeding observed in patients with renal failure.

Platelet Dysfunction

Platelet dysfunction increases with severity of renal insufficiency, although there is no direct correlation between the two parameters.

Platelet Defects

1. Impaired adhesive capability
2. Impaired aggregation

Impaired platelet adhesive capability: Impaired platelet adhesiveness had been considered to be secondary to abnormal vFw on the basis of:

a. Quantitative deficiency of platelet vFw
b. Uremic-induced plasma inhibitor of vFw-GP1b; and
c. Shortening of BT by dDAVP or cryoprecipitate suggesting increased level of vWf which may overcome the inhibitor. However, no consistent abnormality in plasma vWf has been noted.

Impaired platelet aggregation has been found which is secondary to:

a. Diminished concentrations of platelet serotonin and ADP
b. Increased production of thromboxane B_2 (TXB_2)
c. Increased production of prostacyclin (PGI_2)
d. Increased NO production
e. Increased platelet cAmp concentration
f. Plasma metabolites such as urea, creatinine, guanidinosuccinic acid.

Threshold aggregating concentration for collagen, ADP and epinephrine, when used singly or in pairs, were two to three times higher than normal in platelet-rich plasmas from hemodialyzed patients.

Serum TXB_2 concentrations were found to be significantly reduced compared to control in renal failure.

Prostacyclin (PGI_2) inhibits platelets aggregation, and increased vascular PGI_2 production has been demonstrated in patients with severe renal failure. This enhanced production of PGI_2 in uremia appears to be plasma mediated. Studies have demonstrated that uremic plasma stimulates the production of PGI_2 in uremia and appears to be plasma mediated. Studies have demonstrated that uremic plasma stimulates the production of higher concentrations of PGI_2 from cultured pig aortic endothelial cells than does normal plasma. The production of PGI_2 does not appear to be significantly reduced by hemodialysis.

Nitric Oxide

Nitric oxide and NO metabolites may adversely affect uremic bleeding. The evidence is rather subtle. However, it has been noted that BT is prolonged in healthy volunteers inhaling NO. Also monomethyl-L-arginine, and NO inhibitor significantly shortened BT in healthy humans, suggesting a role of NO in primary hemostasis.

Increased production of cAmp may be caused by elevated PTH levels; may be related to impaired TXB_2 production; and does not appear to be corrected by dialysis.

The plasma metabolites have been implicated singly or in combination as possible causes of platelet dysfunction in uremia. This may explain the improvement in platelet function in most patients following hemodialysis or CAPD. In support of this hypothesis, it has been demonstrated that normal platelets, when incubated in uremic plasma, show diminished aggregation. Likewise, uremic platelets, when incubated in normal plasma, show improved aggregation.

Effect of Aspirin on Uremic Bleeding

A special note should be made in this regard. Acetylsalicylic acid (ASA) is sometimes prescribed to reduce thrombosis of the vascular access in patients treated with maintenance hemodialysis. ASA induces a greater prolongation of BT in uremics than in normal subjects.

Summary of Hemostatic Defects and Bleeding Sites in Uremia

Hemostatic Defects

- Abnormal bleeding time
- Platelet dysfunction (Multifactorial)
- Possible vascular factors (Humoral)

Specific Bleeding Sites at Risk

Increased risk	*Spontaneous bleeding*
Venipuncture sites	Intraocular
Peptic ulcer	Intracranial
Rectal ulcer	Pericardial
Angiodysplasia	Mediastinal
	Retroperitoneal

THERAPEUTIC STRATEGIES

A. Control of bleeding
   1. Correction of anemia
   2. Cryoprecipitate
   3. Desmopressin therapy
   4. Conjugated estrogens
   5. Recombinant factor
   6. Dialysis
   7. Avoiding drugs that impair platelet function
   8. Platelet transfusion
B. Treatment of source of bleeding

Control of Bleeding

Correction of Anemia

It has been observed that bleeding time is not shortened until hematocrit is increased above 30 percent. In one study, 6 patients with hemorrhagic complications were transfused with washed packed cells to increase hematocrit to more than 30 percent. In all six patients, the BT was longer than 15 minutes at the time of transfusion. After transfusion, BT was shortened in all but one patient and hemorrhagic manifestations seemed to be reduced in severity in all except the patient whoes BT was unchanged. It is fairly evident that higher the hematocrit, lower is the BT.

To evaluate whether the rise in autologous red cells induced by recombinant erythropoietin has the same effect as that of transfusion in improving hemostasis, seven patients with uremia, severe anemia, prolonged BT and mild bleeding symptoms were treated with erythropoietin of variable doses to achieve 50 percent (D 50) or 100 percent (D 100) of goal hematocrit. BT and platelet adhesion before and after erythropoietin were assessed.

At D 50, BT is shortened in all but one patient, whereas in D 100, BT is shortened in all patients. No difference was found in BT between D 50 and D 100. The bleeding symptoms before erythropoietin administration disappeared during the study period.

Cryoprecipitate

Cryoprecipitate is rich in factor VIII and vWf and has been used effectively both in controlling overt bleeding and in shortening the BT in patients with renal insufficiency. A typical dose of cryoprecipitate is 10 units. This may be repeated every 12 hours. Shortening of BT nadirs between 4 and 12 hours following transfusion and may persist upto 24 hours. Hemostasis is improved to the extent that life-threatening bleeding can be prevented and surgery or a procedure can be performed safely. The mechanism of the correction of bleeding by cryoprecipitate is unknown. Fresh frozen plasma may be used in lieu of cryoprecipitate. However, fresh frozen plasma is not rich in vWf. The major disadvantages of cryoprecipitate or fresh frozen plasma are its short duration of action and the risk of transmission of blood borne diseases.

Desmopressin Therapy

Desmopressin or 1-deamino-8-D-arginine vasopressin (dDAVP), is a synthetic analog of the antidiuretic hormone, vasopressin. Desmopressin effects release of autologous stores of the factor VIII complex (as well as other substances) from endothelial cells. Administration of either intranasal or intravenous dDAVP is associated with a transient elevation in the plasma level FVIII: vWf and the release of larger-than-normal vWf multimers. Unlike vasopressin, dDAVP has little-to-no smooth muscle activity. When given intravenously, the recommended dosage is 0.3 to 0.5 ug of dDAVP per kg of body weight in 30 to 50 ml of saline given over 20 to 30 minutes. Administration can be repeated in 12 hours and perhaps again 12 hours after that. Following two to three successive administrations, endothelial FVIII:vWf stores are depleted and 3 to 4 days are required for repletion. In a number of trials, administration of dDAVP has been associated with shortening of the bleeding time in patients with renal insufficiency. In one report bleeding times were normalized in all 15 patients, 90 minutes port-infusion with dDAVP. No significant changes in factor VIII/vWf associated properties, blood cell counts or coagulation factors were observed. However, a significant increase in platelet serotonin uptake and ATP release was detected after dDAVP treatment. These results indicate that dDAVP blocks vasopressin-induced platelet aggregation in a dose and time dependent fashion. Maximum shortening of the bleeding time typically occurs between 1 and 4 hours after the administration and persist for 4 to 8 hours. Desmopressin, therefore, has been suggested for those patients undergoing an invasive procedure, requiring temporary correction of platelet dysfunction or as the initial therapy in patients with hemorrhagic diathesis. The mechanism of bleeding-time correction is unknown.

The major disadvantages of desmopressin therapy include short duration of action and development of tachyphylaxis as endothelial cell stores are depleted after two 3 successive administrations. There are no consistent side effects associated with administration of this drug except for headache, mild facial flushing, and occasionally mild systemic hypertension. Although dDAVP is an analog of antidiuretic hormone, water retention and hyponatremia are not significant problems in most patients. Care must be taken, nonetheless, when dDAVP is administered to the old persons. Myocardial ischemia and the cerebral vascular thrombosis after the administration of dDAVP have been reported. These cases suggest that caution should be exercised when administering desmopressin to elderly patients with severe atherosclerotic vascular disease.

Conjugated Estrogens

Conjugated estrogen therapy is one of the most exciting advances in the treatment of uremia-associated bleeding. Initial trials were based on the observation that pregnancy and increased blood estrogen levels are associated with shortening of the bleeding time in women with von Willebrand's disease. Subsequently, studies have consistently demonstrated that conjugated estrogen therapy is effective in shortening the bleeding time in uremia and is effective in controlling clinical hemorrhage in this populations.

A single estrogen infusion of 0.6 mg/kg is associated with transient shortening of the bleeding time that is maximum at 24 hours and persists up to 72 hours. The initial effect on bleeding time in seen in approximately 6 hours. Daily estrogen infusion for four to five days results in prolonged shortening of the bleeding time for up to 14 to 25 days. The results are shown in Table 1.

The mechanism of action of estrogen therapy is unknown. Unlike dDAVP and cryoprecipitate, estrogen therapy is not associated with any change in the levels of vWf or in its multimeric structure. It has been postulated that estrogens act to diminish the release of vascular prostacyclin. No significant side effects have been noted with this form of therapy. The major advantages of conjugated estrogens include their long duration of action and few, if any, side effects. Further, the use of conjugated estrogens diminishes the patient's exposure to blood products. The effect of conjugated estrogens on BT in uremics is reversible, and after 25 days all patients had a BT value comparable to the basal value. The pharmacokinetics of conjugated estrogens in uremics is comparable to that of normal subjects.

Recombinant Factor

A single dose of 90 mcg/kg of recombinant factor VIIa (rFVII) (Noroseven®) (Novo Nordisk) may be effective in controlling severe bleeding tendency in renal failure patients not affected by therapy already described. A patient with renal failure and severe pulmonary bleeding was treated with rFVIIa. There was a prompt cessation of the pulmonary bleeding and BT decreased from more than 15 min to 6 min. After, 4th day BT increased to 9.5 min and 24th day more than 15 min, but no over bleeding was observed. However, this drug is not universally available or accepted as an effective therapy in uremic bleeding.

Dialysis

Dialysis treatment has definitely reduced the frequency of uremic bleeding. The majority of reports suggest that the "routine" hemodialysis does not eliminate the bleeding tendency, as dialysis only partially and transiently corrects platelet dysfunction. It should be noted that adequate dialysis is fundamental in providing some protection for uremic patients against hemorrhagic risk. Nevertheless, this treatment alone is not uniformly effective, either in preventing or curing spontaneous or surgical hemorrhages. This is supported by the observation of prolonged bleeding from the puncture sites in the hemodialyzed patients. Although it has been noted that dialysis may improve the bleeding tendency of uremia, there is, additionally, sufficient experience to suggest that hemodialysis with heparin may also increase both the frequency and severity of bleeding in patients who are at increased risk. For example, it appears that intracranial hemorrhage may be both more frequent and more severe in hemodialysis patients than in non-hemodialysis patients, perhaps as a result of repeated intermittent heparinization.

Few studies have been done to examine the validity whether peritoneal membrane would be more efficient than the currently employed hemodialysis membranes in removing the factor(s) that influence platelet function. It has been observed that BT is significantly shorter after a few months of CAPD than in the same patients when

Table 1. Effects of cumulative doses of conjugated estrogen (CE) on bleeding time

Patient No.	*Administration No.*	*Cumulative dose of CE mg*	*Bleeding time min*	
			pre-	*14 days*
1	4	98	21	10
2	4	156	15	7
3	5	180	23	11
4	5	195	>30	15
5	5	153	25	11
6	5	180	25	10
7	5	228	20	9
8	5	138	>30	15
9	4	132	21	9
10	5	195	17	8

Adapted from Vigano et al. with permission.

they were treated with conventional hemodialysis. This might simply reflect the increase in hematocrit level that also has been observed in the same patients.

Avoiding Drugs that Impair Platelet Function

Numerous drugs are associated with prolonged BT. These drugs are presented in Table 2. These drugs should be avoided in uremic patients with bleeding tendency.

Platelet Transfusion

Platelet transfusions have limited value, as transfused platelets become abnormal soon after exposure to uremic plasma. Platelet therapy should be considered only in acute hemorrhagic episodes or if the patient has significant thrombocytopenia.

Treatment of the Source of Bleeding

- *H_2 blocker such as cimetidine (Tagamet*), ranitidine (Zantac*)*
- *GI consultation*
- *Endoscopy*
- *Celiac arteriography*
- *Surgical consultation*

Table 2. Drugs associated with a prolonged bleeding time*

Anti-inflammatory drugs	*Cardiovascular drugs*
Aspirin	Calcium channel blockers
Ibuprofen	Nitroglycerin
Indomethacin	Nitroprusside
Naproxen	Reserpine
Antibiotic Drugs	Miscellaneous Drugs
Ampicillin	Aminocaproic acid
	Chlorpromazine
Carbenicillin	Cocaine
Gentamicin	Cyclosporine A
	Dextran
Moxifloxacin	Furosemide
Nafcillin	Halothane
Nitrofurantoin	Heparin
Penicillin G	Radiographic contrast agents
Piperacillin	Theophylline
Ticarcillin	Vinblastine

* In the presence of a normal platelet count adapted from thrombosis and hemostasis vol 11,1989.

SUMMARY

1. Bleeding is a frequent complication of uremia. Gastrointestinal (GI) bleeding is more common than other types of bleeding. Preexisting GI lesion is a common accompaniment.
2. Prolonged bleeding time is the consistent detectable abnormality.
3. Elevation of hematocrit by packed cell transfusion or erythropoietin decreases BT and is effective in minimizing bleeding.
4. dDAVP or cryoprecipitate is very useful in controlling spontaneous acute GI bleeding or in providing protection against hemorrhages in patients undergoing surgery or a procedure.
5. Conjugated estrogen can be recommended in recurrent but less life-threatening bleeding.
6. In all cases of uremic bleeding dialysis: hemo or CAPD is an insurance for protection against hemorrhagic risk.

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Renal Osteodystrophy

Shalini Sundar, Arnold J Felsenfeld

In chronic renal failure, the classic bone disorder is osteitis fibrosa which develops because of secondary hyperparathyroidism. However, renal osteodystrophy includes not only osteitis fibrosa, a bone disorder that can be entirely explained by hyperparathyroidism but also consists of other bone disorders which include osteomalacia and adynamic bone. Bone is composed of both minerals and organic matrix. The minerals are primarily calcium salts of which calcium hydroxyapatite is predominant. Organic materials which compose the unmineralized matrix include type I collagen, osteocalcin, osteonectin and osteopontin. Bone formation and remodeling are accomplished by cells specific to the bone which are osteoblasts, osteoclasts and osteocytes. Osteoblasts deposit osteoid, which is the unmineralized matrix for new bone and osteoclasts resorb mineralized bone. In contrast to osteoblasts and osteoclasts which are on the bone surface, osteocytes are located within the mineralized bone and are originally derived from osteoblasts. The osteocyte besides being the site of FGF-23 production, acts as a stress sensor and is important in the signal to activate bone remodeling.

When the glomerular filtration rate (GFR) falls to 50 to 60 ml/min, approximately half of patients already have abnormal bone histology. Virtually all patients have abnormal bone histology when the GFR decreases to 25 to 30 ml/min. As renal failure progresses, the capacity to excrete phosphorus decreases and eventually hyperphosphatemia develops. While a high phosphorus concentration may directly increase parathyroid hormone (PTH) secretion, the major effect of a high phosphorus concentration is from a decreased calcemic response to PTH, which in turn increases PTH secretion. Also high serum phosphorus stimulates the production of FGF-23, which suppresses 1,25 dihydroxyvitamin D synthesis, thereby indirectly increasing the secretion of PTH. Finally, metabolic acidosis is another factor which may contribute to the development of bone disease in renal failure.

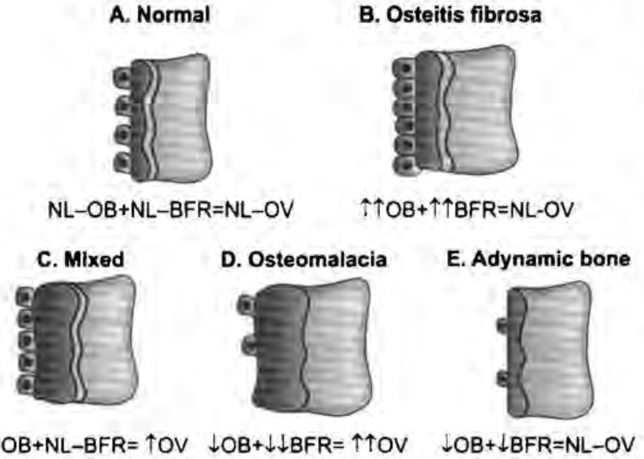
As has been stated, renal osteodystrophy is not a single entity but consists of several distinctly different forms of bone disease (Figs 1A to E). The most common form, osteitis fibrosa results from hyperparathyroidism and is characterized by high bone turnover with increases in the number of osteoblasts and osteoclasts and an increased bone formation rate, all of which are driven by a markedly elevated PTH level. Conversely, osteomalacia is associated with a reduced bone formation rate (mineralization) and osteoid accumulation. The form of osteomalacia associated with aluminum toxicity is characterized by osteoid accumulation with a marked decrease in the osteoblast surface and a severe reduction in mineralization. Another form of renal osteodystrophy called mixed disease, has features of both osteomalacia and osteitis fibrosa. In this disorder, osteoid accumulates and mineralization is decreased relative to the rate of osteoid deposition but in general, mineralization is in the normal range. Moreover, there is not the marked reduction in osteoblasts seen with aluminum-induced "low turnover" osteomalacia. Finally, adynamic bone is characterized by decreased mineralization, a marked reduction in osteoblasts but without overall osteoid accumulation. However, focal areas of osteomalacia are often seen.

I. Pathogenesis of Secondary Hyperparathyroidism (2°HPT)

Hyperparathyroidism develops in renal failure due to multiple factors which include a tendency to develop hypocalcemia, phosphorus retention, a calcitriol deficiency, resistance to the calcemic action of PTH and possibly metabolic acidosis (Table 1). A schematic representation of some of the causes for parathyroid cell proliferation and parathyroid gland hyperplasia is shown in Figure 2.

A. Calcium

Normal calcium balance is maintained as a result of gut absorption, calcium influx to and efflux from bone and calcium excretion and reabsorption by the kidney. As is shown in Figure 2, PTH is the controlling factor for plasma calcium regulation. The relationship between PTH and calcium is a sigmoidal curve and in normal humans, the PTH concentration is approximately 20 to 25 percent of its maximal secretory capacity (Fig. 3). Because of the sigmoidal relationship, a small decrease in serum ionized calcium elicits a relatively large increase in PTH. The increased PTH secretion rapidly restores serum calcium to normal through a combination of events which include increased bone efflux of calcium, increased renal calcium reabsorption and increased phosphorus excretion, with the latter decreasing the serum phosphorus concentration. A delayed effect of increased PTH secretion is an increase in calcitriol production which enhances intestinal calcium absorption. In renal failure, the compensatory mechanism is imperfect because of impaired calcitriol production, a failure to appropriately lower the serum phosphorus and a decreased skeletal response to PTH (Fig. 2). As a result, more PTH is needed to prevent the development of hypocalcemia. Thus, to retard the development of 2°HPT, it is important to maintain a normal serum calcium concentration through adequate calcium intake. But care must also be taken not to produce a state of calcium overload because this can favor the development of adynamic bone and soft tissue calcification.



Figures 1A to E: Schematic representation showing how the relationship between the rate of osteoid deposition (osteoblast) and the bone formation rate affects the osteoid volume. The osteoid volume (OV) is proportional to the rate of osteoid deposition (osteoblasts) and the bone formation rate (BFR), the latter of which is determined by double tetracycline labeling shown as the wavy dark lines. In osteitis fibrosa, an increased osteoid deposition is counterbalanced by an increase in bone formation rate resulting in normal osteoid volume. In mixed uremic osteodystrophy, the rate of osteoid deposition is generally minimally increased and the rate of bone formation is generally in the normal range; thus, an accumulation of osteoid is present. In adynamic bone, both the rate of osteoid deposition and bone formation are decreased proportionally so that osteoid does not accumulate. In "low turnover" osteomalacia, both the rate of osteoid deposition and the bone formation rate are decreased but the former exceeds the latter resulting in osteoid accumulation

B. FGF-23

Fibroblast Growth Factor-23 is a recently discovered regulator of phosphate and calcium metabolism. FGF-23 is a 251 amino acid protein synthesized and secreted by bone cells, mainly osteocytes. FGF-23 exerts its biological effects through activation of FGF receptors whose activation requires the co-factor Klotho. Klotho is a 130-kDa transmembrane ß-glucuronidase that is expressed in the cells of renal tubules, parathyroid glands and the choroid plexus, conferring FGF-23 tissue selectivity despite the ubiquitous expression of FGF receptors.

Table 1. Pathogenesis of secondary hyperparathyroidism

1. Hypocalcemia
2. Phosphorus retention
3. Calcitriol deficiency
4. Skeletal resistance to parathyroid hormone
5. Uremia
6. Metabolic acidosis

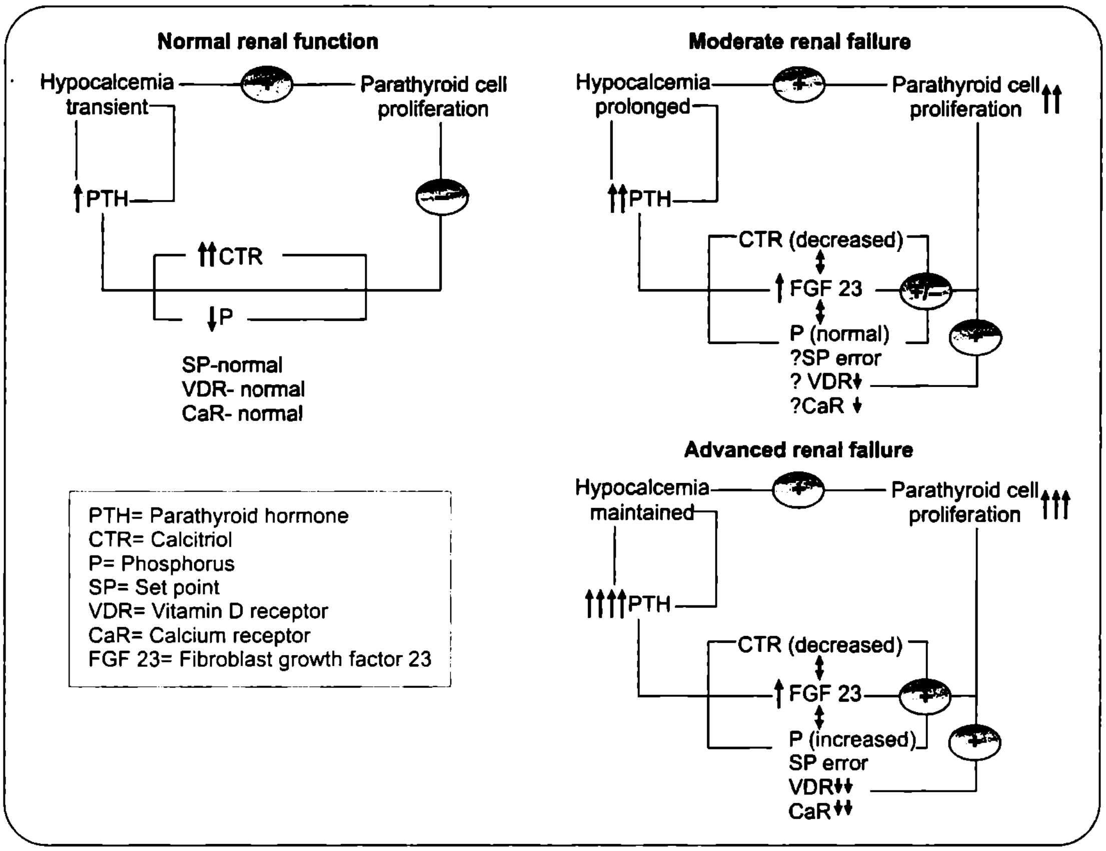


Figure 2: Potential factors that may control or prevent parathyroid cell proliferation in the healthy individual and contribute to the stimulation of parathyroid cell proliferation in patients with renal failure. In healthy individuals, any episode of hypocalcemia should be transient because of the efficiency of the homeostatic system. Moreover, PTH-induced increases in the serum calcitriol level and decreases in the serum phosphorus level should have an anti-proliferative effect on the parathyroid cell. In moderate and advanced renal failure, the calcium homeostatic system becomes progressively less efficient. Decreases in calcitriol production and increases in serum phosphorus levels stimulate PTH secretion and probably stimulate proliferation of parathyroid cells. Finally, in renal failure, decreases in the vitamin D receptor result in less efficient control of PTH secretion and may also contribute to parathyroid cell proliferation

FGF-23 induces phosphaturia by reducing the abundance of the renal sodium phosphorus co-transporter Na/Pi IIa in the proximal tubular cells. FGF-23 also decreases serum calcitriol levels by decreasing renal expression of 1α-hydroxylase. Finally, FGF-23 directly reduces PTH secretion in a dose dependent manner by decreasing PTH mRNA secretion.

In chronic kidney disease (CKD), FGF-23 levels gradually increase with declining renal function. Although the increase in FGF-23 is most pronounced in patients with advanced CKD, it begins at an early stage even when serum phosphorus levels are still normal. In CKD patients, there is a deficiency of Klotho cofactor, which results in end-organ resistance to the phosphaturic stimulus of FGF-23. This results in increased FGF-23 secretion, and also higher FGF-23 values may reflect a physiological attempt to stabilize serum phosphorus values within a 'normal' range (2.5 to 4.5 mg/dL) until advanced CKD develops. Upregulation of FGF-23 also inhibits renal 1α-hydroxylase and is probably responsible for the calcitriol deficiency seen in early CKD. Calcitriol deficiency induces PTH secretion both directly and indirectly (through reduced gastrointestinal calcium absorption and subsequent hypocalcemia). Even though FGF-23 directly inhibits PTH secretion in normal individuals, there are increased levels of both FGF-23 and PTH in CKD patients, indicating that FGF-23 fails to suppress PTH secretion in CKD. This result is likely

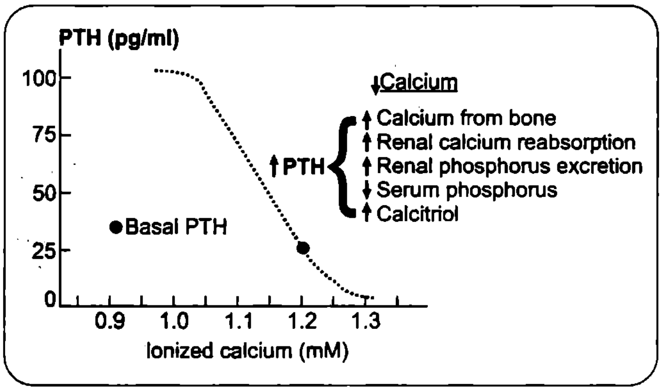


Figure 3: The PTH response to hypocalcemia. Shown is the sigmoidal PTH-calcium relationship and how a small reduction in serum calcium elicits a large increase in PTH. The increase in PTH functions to restore serum calcium by increasing calcium efflux from bone, by increasing renal calcium reabsorption, increasing renal phosphorus excretion, decreasing serum phosphorus, and increasing calcitriol production

due to a decrease in Klotho in CKD patients. In clinical studies in CKD patients, increased FGF-23 levels were independently associated with faster progression of CKD, resistance to treatment of 2°HPT, left ventricular hypertrophy and increased cardiovascular mortality in dialysis patients.

C. Phosphorus

The usual oral intake of phosphorus ranges from approximately 800 to 1500 mg/day and phosphorus balance is maintained by urinary excretion of phosphorus. Even in renal failure intestinal phosphorus absorption is maintained between 60 percent and 70 percent so that the amount absorbed increases linearly as phosphorus intake is increased. As the GFR decreases, the capacity for renal phosphorus excretion decreases and eventually hyperphosphatemia develops. In early renal failure, the serum phosphorus level is usually normal because of increases in PTH and FGF-23. Increases in FGF-23 production helps to maintain a normal serum phosphorus level but at the cost of a decreased serum calcitriol level. Even though serum phosphorus is normal in early to moderate CKD, a strong argument can be made that it is not appropriately decreased for the high PTH level. At a GFR of approximately 25 to 30 ml/min, hyperphosphatemia develops because high PTH levels and FGF-23 cannot further increase renal phosphorus excretion (Fig. 2).

Hyperphosphatemia increases serum PTH levels as a result of both indirect and direct mechanisms. Indirect mechanisms include the inhibition of calcitriol synthesis, a decreased skeletal response to PTH which promotes the development of hypocalcemia, and elevated FGF-23 levels with resultant calcitriol suppression. Hyperphosphatemia may also have a direct effect on PTH synthesis and secretion independent of serum calcium and calcitriol levels. All these factors increase PTH secretion and result in parathyroid gland hyperplasia. In renal failure, the magnitude of hyperphosphatemia is exacerbated by the failure to restrict dietary phosphorus, poor compliance with phosphate binders and sometimes inadequate dialysis.

D. Vitamin D

In humans, the two sources of vitamin D are vitamin D$_2$ (ergocalciferol) and vitamin D$_3$ (cholecalciferol). Ergocalciferol is synthesized in plants and yeast and represents a dietary source. However, 90 percent of human vitamin D requirements come from exposure of the skin to ultraviolet - β radiation. Vitamin D is hydroxylated in the liver to 25(OH) vitamin D and further hydroxylated in the kidneys to 1,25(OH)D$_2$ or D$_3$ (calcitriol).

In healthy subjects, 25(OH)D values below 20 ng/ml are associated with increases in PTH values. Current recommendations are to maintain a 25(OH)D level greater than 30 ng/ml. In the past, 25(OH)D values greater than 10 ng/ml have been shown to be sufficient to prevent rickets and osteomalacia. Thus, vitamin D deficiency was defined as 25(OH)D values less than 10 ng/ml. However, because recent studies have indicated that 25(OH)D values greater than 30 ng/ml are desirable, 25(OH)D values between 10 and 30 ng/ml have been classified as vitamin D insufficiency and that term will be used in this chapter. In the majority of CKD patients, vitamin D levels are below 30 ng/ml regardless of the geographic location. Suboptimal levels of vitamin D contribute to the development of 2°HPT through reduced intestinal calcium absorption and increased PTH secretion. Besides its role in mineral homeostasis, vitamin D has recently been recognized to have several extraskeletal effects, including modulation of endothelial and immune function, inflammatory responses and cell cycle regulation, and renin secretion.

The active form of vitamin D derivative is calcitriol, which enhances calcium absorption in the gut, calcium reabsorption in the kidney, and the calcemic response to PTH. Calcitriol deficiency is observed in the early stages of CKD. Traditionally it has been thought that the low calcitriol levels are due to a reduced nephron mass. However, it was not understood why early stages 2 to 3 of CKD should result in low 1α-hydroxylase levels, whereas secretion of erythropoietin remained unaffected. But the explanation is that upregulation of FGF-23 levels inhibits renal 1α-hydroxylase and results in decreased calcitriol synthesis. Also, in CKD patients the production of calcitriol appears to be more substrate dependent (25OHD) than in normal humans in whom calcitriol production is maintained by high PTH values and decreases in serum phosphorus.

Calcitriol is also important because of its direct effect on PTH synthesis. It suppresses PTH transcription and regulates vitamin D receptor and calcium sensing receptor gene transcription in the parathyroid gland. Thus, a calcitriol deficiency results in the loss of the normal suppressive effect of calcitriol on PTH secretion. Moreover, when parathyroid gland hyperplasia develops, there is a further decrease in vitamin D receptors in the hyperplastic tissue. Thus, supraphysiologic levels of calcitriol may be required to suppress parathyroid hyperplasia in renal failure. Moreover, in renal failure, uremic toxins may result in changes in the vitamin D receptor and also produce postreceptor effects and thus function to limit the effectiveness of calcitriol.

E. Skeletal Resistance to the Calcemic Action of PTH

In azotemic patients, a wide range of PTH values are observed. It has been shown that elevated intact PTH values of 150 to 300 pg/ml (normal 10 to 65 pg/ml) are necessary to maintain a normal osteoblast surface and bone formation rate. These results confirm the presence of skeletal resistance to PTH in uremia. However, part but not all of the reason for the higher PTH values is the increase in inactive N-terminal PTH fragments in renal failure (see section on diagnosis of renal osteodystrophy).

F. Uremia

Even after important factors such as calcitriol deficiency, hypocalcemia and phosphorus retention are treated, the effect of uremia may contribute to the development of 2°HPT.

G. Metabolic Acidosis

The capacity of the kidney to excrete acid progressively falls as the GFR decreases and thus metabolic acidosis develops. Retained acid must be buffered and the bone is a major factor in the buffering of the acidosis. Metabolic acidosis also enhances urinary calcium excretion and increases efflux of calcium from bone. Acidosis may also directly affect PTH secretion. Studies have shown that a decrease in blood pH, induced by metabolic acidosis can increase PTH secretion. A potential mechanism for the effect of acidosis on PTH secretion is that a decrease in pH (acidosis) renders the calcium sensing receptor less sensitive to activation by calcium. Conversely, an increase in pH (alkalosis) produces the opposite effect.

PREVALENCE OF DIFFERENT TYPES OF RENAL BONE DISEASE

Disorders of high bone turnover (osteitis fibrosa and mixed osteitis fibrosa with osteomalacia) predominate in adults with CKD stages 3 to 5 (58 percent of patients), hemodialysis patients (69 percent of patients) and children with CKD stages 5 and 5D (61 percent of patients). Conversely, disorders of low bone turnover (adynamic bone and osteomalacia) predominate in peritoneal dialysis patients (55 percent of patients).

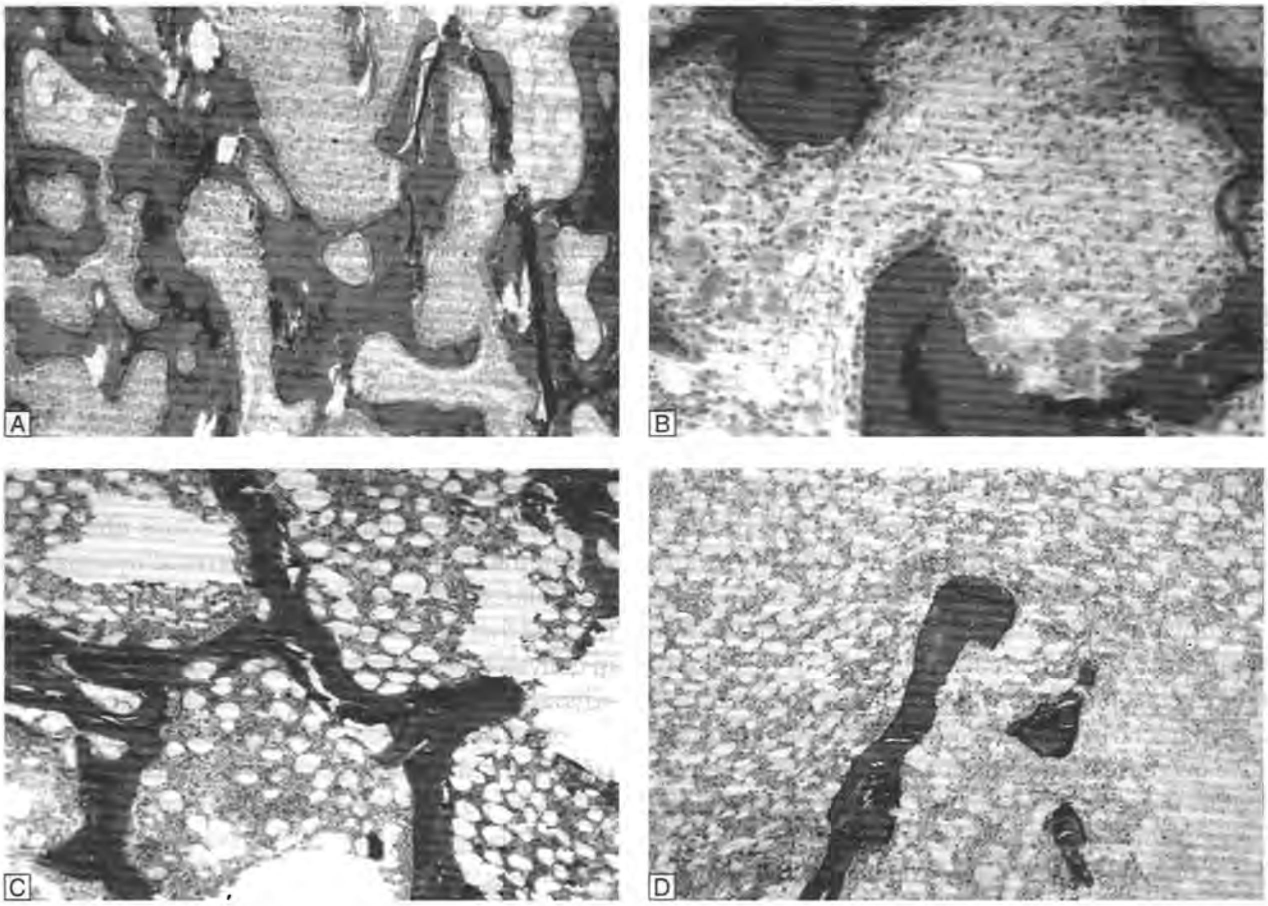
II. Classification of Renal Osteodystrophy

A. Osteitis Fibrosa

As stated previously, 2°HPT is responsible for the development of osteitis fibrosa which is characterized by an increased rate of bone formation, increased bone resorption and the presence of fibrosis in the bone marrow space. Osteoid seams are numerous and covered by osteoblasts (Figs 4A and B). As illustrated in Figure 1, the osteoid width is not increased because the increased rate of osteoid deposition by osteoblasts is counterbalanced by an increased rate of bone formation. The latter is generally shown by tetracycline labeling in which two time-spaced doses of tetracycline are given before the bone biopsy. As a result of the fluorescent properties of tetracycline and its deposition at the mineralization front, the distance between the two tetracycline labels divided by the number of days permits the calculation of the rate of mineralized bone being formed per day at each site. When the number of tetracycline labels and the distance between labels are averaged over the entire bone surface, the bone formation rate can be calculated. In osteitis fibrosa, osteoclasts as well as resorption cavities are increased (Fig. 4B). The marrow fibrosis is first observed in areas of increased bone resorption, and then progresses to peritrabecular areas. As the severity of hyperparathyroidism increases, areas of fibrosis bridge or connect the separate spicules of trabecular bone. The final stage seen with severe hyperparathyroidism is consolidation of large areas of the bone marrow with fibrosis (Figs 4A and B). Osteitis fibrosa is also characterized by the presence of woven bone in contrast to the usual lamellar pattern of bone seen with normal matrix deposition.

B. Mixed Osteitis Fibrosa-Osteomalacia (Mixed Bone Disease)

As shown in Figure 1, mixed bone disease is characterized by features of both osteitis fibrosa and osteomalacia.



Figures 4A to D: Goldner-stained examples of bone histology. A. Osteitis Fibrosa (low magnification) – large areas of consolidated bone marrow fibrosis, numerous osteoclasts (multinucleated giant cells) and several osteoid seams covered with osteoblasts (orange colored seam covered with a single layer of cells) are seen. In the top right corner, an area of normal bone marrow is present. **B. Osteitis Fibrosa** (high magnification) - multiple osteoclasts in a resorption cavity are seen in the lower right and an osteoid seam with osteoblasts is seen in the upper right. Bone marrow fibrosis is also present throughout. **C. Osteomalacia** (low magnification) – multiple, broad osteoid seams devoid of osteblasts are seen throughout and cover most of the bone surface. The bone marrow space is normal. **D. Adynamic Bone** (low magnification) – bone with thin osteoid seams but without osteoblasts is seen in the larger bone spicule on the left. In the two smaller bone spicules on the right, broad osteoid seams devoid of osteoblasts are suggestive of focal osteomalacia. The bone marrow space is normal (*For color version, refer to plate 2*)

Osteoid accumulates because the rate of osteoid deposition exceeds the rate of bone formation (mineralization). However, while the rate of bone formation is less than that of osteoid deposition, it is generally in the normal range and not decreased as is seen in "low turnover" osteomalacia.

In the predialysis patient, mixed bone disease is often associated with hypocalcemia. It has also been associated with profound metabolic acidosis in the predialysis patient. In these patients, the increased incidence of osteomalacia could be from increased renal losses of phosphorus and calcium, resulting in hypocalcemia and a relative hypophosphatemia. Finally, mixed bone disease can be seen in dialysis patients with osteitis fibrosa who are exposed to aluminum. In these patients, the aluminum decreases the bone formation rate, but the markedly increased PTH levels functions to protect against the development of "low turnover" osteomalacia. However, "low turnover" osteomalacia will develop if the aluminum exposure is ongoing or if these patients undergo parathyroidectomy for their hyperparathyroidism.

C. "Low Turnover" Osteomalacia (Aluminum Bone Disease)

Osteomalacia is caused by defective mineralization of the bone. In the form of "low turnover" osteomalacia in dialysis patients, both osteoid deposition and bone mineralization are decreased and wide osteoid seams develop because the rate of bone formation (mineralization) is decreased more than the rate of osteoid deposition (Fig. 1). "Low turnover" osteomalacia is also characterized by a decrease in osteoblasts and a relative decrease in the number of osteoclasts (Fig. 4C).

Before the era of hemodialysis, osteitis fibrosa existed alone or in combination with osteomalacia (mixed bone disease). "Low turnover" osteomalacia was not observed in azotemic patients before the availability of hemodialysis. As was first noted in Newcastle, England in the late 1960s, the incidence of "low turnover" osteomalacia began to increase after six months of dialysis and further increased with the duration of dialysis. Subsequently, it was noted that the outbreak of "fracturing osteodystrophy" was associated with the presence of aluminum in the dialysate water. In addition to the epidemic form of osteomalacia which was due to aluminum in the dialysate water, sporadic forms of the disorder were noted in some patients, generally after 5 to 10 years of hemodialysis. The sporadic form of "low turnover" osteomalacia could often be attributed to the total burden of aluminum-containing phosphate binder or as a result of the enhanced intestinal aluminum absorption by concomitant use of citrate with an aluminum containing phosphate binder.

The presence of relatively low PTH values also favors the deposition of aluminum on the bone surface and enhances the toxic effects of aluminum. Patients with diabetes mellitus may have a higher risk for aluminum bone disease because the relative PTH deficiency commonly seen in the azotemic diabetic patient is associated with low bone turnover and favors the development of aluminum accumulation on the bone surface.

More than 90 percent of the aluminum in the body is bound, mostly to transferrin. Thus, the amount of aluminum available for removal through dialysis is minimal and dialysate aluminum levels >5 to 10 ug/L result in the transfer of aluminum to the patient.

D. Adynamic Bone

Adynamic bone is characterized by a normal osteoid volume which results from a proportional decrease in the bone formation rate and the rate of osteoid deposition (Fig. 1). However, focal osteomalacia is often present. Adynamic bone is also characterized by a paucity of osteoblasts and osteoclasts (Fig. 4D). Previously, it was thought that the most frequent cause of adynamic bone in dialysis patients was aluminum toxicity. Patients with adynamic bone caused by aluminum accumulation are often symptomatic because of skeletal problems. However, today the majority of patients with adynamic bone have no evidence of aluminum overload. Even in the predialysis patients who never have received aluminum-containing phosphate binders, adynamic bone is often present. Overt skeletal symptoms are absent. Factors associated with adynamic bone include a relative lack of PTH, calcium treatment, diabetes, calcitriol treatment, continuous ambulatory peritoneal dialysis (CAPD) and older age (Table 2). The individual factors which have been associated with the development of adynamic bone are discussed below:

1. *PTH and Calcium*—It is difficult to separate the effect of a relatively low PTH level from that of high

calcium exposure because the latter functions to suppress PTH. Since higher than normal PTH values are needed to maintain normal bone remodeling, a relative deficiency of PTH is often associated with reduced bone remodeling.

2. *Calcitriol* treatment has been associated with an increased incidence of adynamic bone. Its effect may be due to calcitriol induced hypercalcemia and a reduction in PTH levels, but may also be due to a direct effect of calcitriol.
3. *Type of dialysis*—CAPD patients have continuous exposure through the dialysate to a high calcium concentration in the dialysate. In most studies, PTH levels are lower in CAPD than hemodialysis patients, and could account for the higher incidence of adynamic bone in CAPD patients.
4. *Age* may be an independent risk factor for the development of adynamic bone. The incidence of adynamic bone has been shown to be higher in the older population. The increased incidence may be due to an inherent decrease in bone remodeling with a diminished response to PTH, reduced circulating sex steroids and oxidative stress in the older population. Also, the spontaneous reduction in caloric intake in the elderly is associated with lower serum phosphorus levels resulting in a relatively low PTH level.
5. *Diabetes*—Patients with diabetes have a higher incidence of adynamic bone and also have a greater incidence of a relative PTH deficiency. There are several reasons which could be responsible for the relative PTH deficiency in the azotemic diabetic patient: (1) extensive vascular disease already present in the azotemic diabetic patient may result in the lack of vascular infrastructure needed for the development of parathyroid gland hyperplasia; (2) hyperglycemia which has been shown to decrease PTH secretion in vitro; and (3) advanced glycosylation end products may retard parathyroid cell proliferation.

Table 2. Factors that favor the development of adynamic bone

1.	Aluminum exposure
2.	Relative deficiency of parathyroid hormone
3.	High calcium dialysate and calcium administration
4.	Calcitriol treatment
5.	CAPD
6.	Older age
7.	Diabetes

E. Dialysis-related Amyloid Bone Disease

Beta 2 microglobulin is a low molecular weight protein that is expressed on the surface of all nucleated cells. It normally circulates freely in the circulation without binding to other proteins. Ninety-five percent of beta 2 microglobulin is filtered through the glomerulus and it is completely absorbed and degraded in the proximal tubule. The remaining 5 percent is cleared at unknown extrarenal sites. Renal failure results in accumulation of beta 2 microglobulin.

The daily normal production of beta 2 microglobulin is about 2 to 3 mg/kg or approximately 200 mg/day or 1400 mg/week. In the literature from the 1990s, the capacity of hemodialysis to remove beta 2 microglobulin was 400 to 600 mg/week. For peritoneal dialysis it was approximately 300 mg/week. The incidence of amyloid related bone disease directly correlates with duration of dialysis. Beta 2 amyloid primarily deposits in osteoarticular tissues and synovia which are rich in collagen, presumably because of the high affinity of beta 2 amyloid for collagen. In a postmortem study from the early 1990s, the incidence of amyloid related bone disease was 21 percent with <2 years, 50 percent with 4 to 7 years, 90 percent with 7 to 13 years, and 100 percent after 13 years of dialysis.

The risk of development of amyloid related bone disease is greater in patients starting dialysis after the age of 40 than in younger patients. Some studies have suggested that the use of biocompatible dialysis membranes reduce the incidence of dialysis amyloidosis. Also, high flux dialysis membranes have a greater rate of convective transport and better clearance of beta 2 microglobulin. In recent studies, the prevalence of dialysis related amyloid bone disease has markedly decreased probably because dialysis is more frequently performed with high flux biocompatible dialysis membranes.

III. Clinical Features of Renal Osteodystrophy

Clinical features that are specific for a form of osteodystrophy are infrequent. However, severe bone pain with fractures is characteristic of aluminum bone disease, but in general it is difficult to make a diagnosis solely by clinical features.

Bone pain is often present and is associated with weight bearing activity and aggravated by sudden changes in position. Such pain appears to be common to all forms of renal osteodystrophy. Most bone pain occurs in the back and lower extremities. Except for the aluminum bone disease, the degree of bone pain in general, does not correlate with extent of radiographic abnormalities.

Fractures are more common in aluminum bone disease than in other forms of renal osteodystrophy. In the past, aluminum bone disease was also known as "fracturing osteodystrophy". Recurrent fractures with minimal trauma and sometimes even in the absence of trauma are common in aluminum bone disease. Spontaneous improvement of bone pain was rare. The rib, vertebra, femur, humerus and metatarsal bones are common sites of fractures in aluminum bone disease.

Vascular calcifications are commonly seen in patients with CKD and in dialysis patients. Studies have shown that vascular calcifications are most advanced in patients with adynamic bone probably because there is a reduced capacity to incorporate calcium into the bone compartment. Thus, systemic exposure to calcium via the use of high calcium dialysate, excessive calcium-containing phosphate binders and/or active vitamin D sterols, probably increase the risk of ectopic, and particularly vascular calcifications.

Proximal muscle weakness characterized by difficulty in combing or setting hair, climbing stairs and rising from a chair is common in all forms of renal osteodystrophy. However, the pathogenesis is not well elucidated and it is often difficult to differentiate among disuse atrophy, specific muscle lesions and malnutrition.

Skeletal Deformity is more common in children than in adults. Before the closure of the growth plate in children, growth retardation is common and epiphyseal slipping is sometimes reported. Skeletal deformity can occur in adults with severe osteomalacia due to aluminum toxicity. In such a situation, vertebral and rib fractures have been known to result in deformity of the thoracic spine and pelvis.

Pruritus is often seen in the azotemic patient and has been attributed to the deposition of calcium and phosphorus under the skin. It has been associated with high serum phosphorus levels and is common in all forms of renal osteodystrophy.

Neurologic manifestations are common in severe hyperparathyroidism. The mental changes include loss of enthusiasm, inability to concentrate and depression. Dialysis dementia appears to be unique to severe aluminum toxicity and in addition to the dementia, other signs include stuttering and stammering speech or even total inability to speak, hallucinations, paranoid ideation, twitching, myoclonic jerks and seizures.

Calciphylaxis is due to tissue ischemia from systemic medial calcification of the small to medium sized arteries. It was initially reported in dialysis patients with severe 2°HPT. It is now more common in obese patients as the calcified blood vessels in these patients fail to provide sufficient blood supply, predisposing to tissue ischemia. Ischemic necrosis of the dermis, subcutaneous fat and sometimes muscle are manifestations of the disease. In patients with severe 2°HPT, involvement of the hands, fingers and lower extremities is common and some patients have recovered after parathyroidectomy. A more proximal form of this disease in obese dialysis patients has been reported in which ischemic necrosis is in the abdominal fat, breast and buttock. This proximal form is generally not associated with severe 2°HPT and does not improve with parathyroidectomy. Other treatment options include lowering the phosphorus levels with the use of noncalcium containing phosphate binders and more recently, the use of sodium thiosulfate. Thiosulfate increases the solubility of calcium and phosphorus deposits and there have been many case reports showing that thiosulfate is effective in improving and even resolving the manifestations of calciphylaxis. However, a prospective study still needs to be performed. Thiosulfate is given intravenously after hemodialysis sessions in doses ranging from 5 to 25 grams. The duration of treatment has extended for six months and sometimes even longer. The major side effect has been an increased anion gap metabolic acidosis which probably originates from sulfate retention.

Beta 2 amyloidosis—Carpal tunnel syndrome is the most frequent presentation in beta 2 amyloidosis. Amyloid deposition often produces a scapulohumeral periarthritis and a painful spondyloarthropathy of the lower cervical spine due to narrowing of the disk space with an associated radiculopathy. Effusions of the knee and shoulder joints have also been reported. Bone cysts occur mostly in the ends of long bones and carpal bones and may be associated with pathologic fracture.

IV. Diagnosis of Renal Osteodystrophy

A. Biochemical Diagnosis Test

1. Parathyroid Hormone

First-generation PTH assays were radioimmunoassays using polyclonal antibodies directed mainly against carboxy-terminal PTH. In addition to 1-84 PTH, these assays measured carboxy terminal fragments that have a longer half-life than 1-84 PTH and also accumulate in CKD patients. Therefore, PTH concentrations measured with these assays were always greatly increased in CKD patients. During the mid-1980s, a second-generation PTH assay, the Allegro intact assay became available. The Allegro assay was a sandwich assay that used antibodies directed against both carboxy-terminal and amino-terminal sites. The amino-terminal epitopes recognized by this assay were after the first six amino acids. Subsequently it was found that, in addition to the 1-84 PTH, the Allegro assay also measured large, truncated, amino-terminal PTH fragments of which 7-84 PTH is the prototype. Subsequently, it was found in dialysis patients that these large non 1-84 fragments account for approximately 50 percent of the measured PTH. Moreover, 7-84 PTH exerts effects that are opposite to those of 1-84 PTH and results in a decrease in serum calcium and urine phosphorus and also inhibits bone resorption. A third generation PTH assay was developed in 1999 and uses anti-amino-terminal antibody directed against the first several amino acids (1 to 4), and thus, does not measure 7-84 PTH. Currently, it is not clear whether the third generation assays correlate better with bone turnover than second generation PTH assays. The KDOQI guidelines acknowledged the potential advantage of third-generation PTH assays, but the guidelines recommended measuring PTH in CKD patients by means of a second-generation assay until more definitive studies have been published. Also important is that studies have found significant variability in PTH assays owing to both antibody specificity and reasons of standardization. Based on this, it has been recommended that the cut-off values for PTH should depend on the particular PTH assay being used. Because PTH values vary with the PTH assay being used, the KDIGO guidelines established in 2009 do not recommend a specific PTH value, but rather state that the goal for PTH in dialysis patients should be a PTH value of two to nine times the upper limit of normal for the PTH assay being used in that dialysis patient.

As a result of studies performed in dialysis patients, several guidelines for the interpretation of PTH levels have evolved. It should be noted that these results are based on the first intact PTH assay (Allegro) that is no longer commercially available (see Souberbielle in recommended reading): a) PTH values >450 pg/ml are almost 100 percent predictive of osteitis fibrosa or mixed disease; b) PTH levels below 100 to 150 pg/ml (normal 10 to 65 pg/ml) are associated with a decreased likelihood of osteitis fibrosa or mixed disease, and an increased incidence of low-turnover bone disease (adynamic bone or osteomalacia); and c) intermediate PTH levels (150 to 450 pg/ml) do not predict the bone turnover state because high turnover (osteitis fibrosa or mixed disease) and low turnover (adynamic bone or osteomalacia) bone disease can be seen at these PTH levels. It is also important to note that these PTH values refer to patients not receiving calcitriol or cinacalcet therapy.

2. Serum Chemistries

Serum calcium and phosphorus levels by themselves are not particularly helpful for the diagnosis of various bone diseases. But a high serum calcium concentration associated with a low PTH value is characteristic of "low turnover" osteomalacia or adynamic bone. The hypercalcemia develops because of the low capacity for bone to buffer a calcium load. However, hypercalcemia can also develop in patients with severe osteitis fibrosa, even in the absence of calcitriol treatment, because of the marked hyperparathyroidism.

3. Diagnosis of Aluminum Bone Disease

Measurement of serum aluminum is the first step in the diagnosis of aluminum bone disease. Values less than 5 to 7 μg/L are seen in normal individuals but in the dialysis patient, values below 20 to 30 μg/L are acceptable. Serum values above 100 to 125 μg/L are consistent with aluminum toxicity or recent exposure to aluminum.

The desferrioxamine (DFO) challenge test is used to diagnose aluminum toxicity. The administration of DFO removes aluminum from tissues and increases serum aluminum levels. Thus, 8 to 24 hours after the administration of 40 mg/kg of DFO, an increase in serum aluminum of 100 μg/L in patients with PTH values <200 pg/ml has been shown to have a specificity of greater than 90 percent in hemodialysis and peritoneal dialysis patients, with a sensitivity of approximately 70 percent for hemodialysis and 50 percent for CAPD patients. The sensitivity of the DFO challenge test is much lower in patients who had been withdrawn from aluminum for more than six months presumably because less bone aluminum is available for chelation. D'Haese et al used a low dose of DFO, 5 mg/kg, to test for aluminum toxicity. They showed that an increase in serum aluminum >50 µg/L combined with a serum PTH less than 150 pg/ml was associated with a high risk of aluminum toxicity.

Aluminum bone disease is now rarely seen in dialysis patients in the developed world. However, it may still be seen in areas in which water purification methods are not adequate. Osteomalacia is also sometimes seen in geographic areas in which the aluminum concentration of the domestic water supply is not high, but periodic spikes in the aluminum concentration occur because aluminum sulfate (alum) is added to the domestic water supply after heavy rains to precipitate flocculent material present.

4. *Serum Markers for Bone Formation*

The most sensitive and reliable diagnostic bone marker for bone formation has been reported to be bone specific alkaline phosphatase. Total alkaline phosphatase is also helpful in the diagnosis of the different forms of bone disease provided that other sources of alkaline phosphatase such as intestine and liver have been excluded. Bone specific alkaline phosphatase (bAP) shows a higher correlation with tetracycline-based bone formation rates than does PTH. The combination of bAP with PTH improves the sensitivity, specificity and the predictive value in the diagnosis of bone turnover. When there is a dissociation between the two parameters, the sensitivity of bAP was higher than that of PTH, and it is thus a better indicator of bone remodeling. Conversely, a low bAP has a comparable efficacy with PTH in the diagnosis of adynamic bone.

5. *Beta 2 Amyloidosis*

Blood levels of beta 2 microglobulin are not a useful marker for the diagnosis of dialysis related amyloidosis. Tissue from synovial biopsies or joint aspirations is needed for a definite diagnosis. Beta 2 microglobulin amyloid is congo red positive and under polarized light, shows an apple green birefringence. Under electron microscopy, nodules are composed of short, thick curvilinear fibrils aligned in parallel and aggregated in bundles.

B. Radiography

Bone mineral density testing should not be performed routinely in patients with advanced CKD because it does not predict fracture risk as it does in the general population. Moreover, bone mineral density does not predict the type of renal osteodystrophy. However, X-rays may be used as an adjunct to help make the diagnosis of renal osteodystrophy.

1. *Osteitis Fibrosa*

Subperiosteal, intracortical and endosteal surface erosion of the cortical bone is the hallmark of bone resorption. The presence of subperiosteal erosions on the radial surface of the middle phalanges of second and third digits of the dominant hand have been stated to be the earliest X-ray change. These early changes then progress to involve other digits and bones.

2. *Osteomalacia and Adynamic Bone*

There are not well-defined radiolographic criteria for the diagnosis of adynamic bone but there are some relatively specific findings for diagnosis of osteomalacia. The overall picture is thinning of the cortex. Looser zones are sometimes present in acute phase of osteomalacia; in more chronic disease, osteopenia is often present, but specific diagnostic criteria are lacking. Moreover, osteomalacia may be misdiagnosed as osteitis fibrosa because old resorption cavities are filled with osteoid. Because osteoid is radiolucent, only the resorption cavities are seen by X-ray.

3. *Beta 2 Amyloidosis*

The presence of bone cysts without subperiosteal erosion is highly suggestive of amyloid related bone disease. Scintigraphic studies with imaging of beta 2 microglobulin deposits by injection of either I-131 labeled beta 2 microglobulin or I-123 labeled serum amyloid P component have been used for the diagnosis of beta 2 amyloidosis. In these studies, beta 2 amyloid deposits were often detected before the development of clinical signs and symptoms and X-ray changes.

C. Bone Biopsy

Bone biopsies are now performed infrequently and the processing and interpretation of bone biopsies are done at a limited number of specialized centers. Nevertheless, bone biopsy may be required to make a definitive diagnosis of renal osteodystrophy.

Indications to perform bone biopsy include:

a. Unexplained fractures
b. Persistent bone pain
c. Unexplained hypercalcemia or hypophosphatemia
d. Possible aluminum toxicity
e. Prior to therapy with bisphosphonates in patients with CKD.

KDIGO has suggested that bone biopsies in patients be classified based on turnover, mineralization and volume. Turnover may be abnormally low to very high, and is measured by tetracycline labeling. Mineralization is measured by osteoid maturation time or by mineralization lag time. The classic disease with an abnormality in mineralization is osteomalacia, in which the bone-formation rate is low and the osteoid volume is high. Bone volume on the other hand, represents the balance between bone formation and resorption. When the former exceeds the latter, bone volume increases. Bone volume decreases when bone resorption exceeds formation. Normal or increased bone volume might suggest a decreased fracture risk, but the quality of bone, as reflected by bone turnover and adequacy of mineralization are also important determinants of bone histomorphometry.

V. Treatment of Renal Osteodystrophy

A. Predialysis Patient

In predialysis patients with a GFR <60 ml/min, consideration should be given to start treatment to prevent the development of 2°HPT. The goal of treatment in these patients is to protect the bone against progression of hyperparathyroidism and to prevent parathyroid gland hyperplasia. To accomplish this goal, it is necessary to control the serum phosphorus, to maintain normal serum calcium values and to treat elevations in PTH. KDOQI recommends a goal PTH of <70 pg/ml in stage 3 CKD and PTH < 110 pg/ml in stage 4 CKD patients. Conversely, KDIGO guidelines state that the optimal PTH value is unknown for stage 3 and 4 CKD. However, they do suggest that patients with intact PTH values above the upper limit of normal for the assay be evaluated and treated for hyperphosphatemia, hypocalcemia and vitamin D deficiency.

Control of serum phosphorus is important to retard progression of 2°HPT. It could be argued that in the presence of an elevated PTH, normal serum phosphorus indicates an inappropriate renal response and might be indicator of an increased phosphorus burden. Also in early CKD, FGF-23 levels rise to maintain a normal phosphorus level. Future studies should be performed to determine the role of dietary phosphorus restriction or phosphate binders in stage 3 CKD. There is little question that once hyperphosphatemia develops, phosphate binders must be started. Studies in stage 4 and 5 CKD patients have also shown that special low protein diets which are low in phosphorus but are supplemented with essential amino or ketoacids decrease PTH values in existing hyperparathyroidism and preserve renal function. Such an approach could be considered to prolong life in symptomatic patients with advanced CKD for whom dialysis is not available because of logistical or financial reasons.

Maintenance of a normal serum calcium value is also important to retard the development of hyperparathyroidism and may also prevent the development of the mixed form of renal osteodystrophy in which osteitis fibrosa is combined with osteomalacia. Several studies in predialysis patients have shown that hypocalcemia is associated with an increased osteoid seam width.

In addition to restricting or binding phosphorus and maintaining a normal serum calcium, progressive hyperparathyroidism can also be controlled by the use of vitamin D metabolites. It has been shown in prospective studies that a low dose of calcitriol or active analogues can successfully control or retard the progression of hyperparathyroidism. Studies have also shown that calcitriol does not produce any deterioration in renal function provided that hypercalcemia is prevented. However, calcitriol treatment may increase serum creatinine values because calcitriol inhibits renal tubular creatinine secretion.

B. Dialysis Patient

In the dialysis patient, the treatment goal is slightly different than in the predialysis patient. Often parathyroid gland hyperplasia with increased PTH secretion is established and thus the goal is to reduce PTH secretion and retard further growth of the parathyroid gland. It is essential that hyperphosphatemia be controlled and normal serum calcium should be maintained. Because of skeletal resistance to PTH, dialysis patients need a higher than normal PTH to maintain normal remodeling. KDOQI recommends a goal PTH between 150 to 300 pg/ml. However, KDOQI guidelines were based somewhat on findings derived from a second generation PTH assay that is no longer available. In addition there are data suggesting significant variability with PTH results among the different assays. This led to the KDIGO to suggest maintaining the PTH levels between two to nine times the upper normal limit for the assay that is being used. Treatments for hyperparathyroidism in the dialysis patient are shown in Table 3 and discussed below.

1. Control of Phosphorus

Control of phosphorus reduces PTH levels and also likely prevents vascular and metastatic calcifications. Moreover, if calcitriol is needed for treatment of severe 2°HPT, control of hyperphosphatemia is necessary to optimize the response to calcitriol. KDOQI recommends maintaining a phosphorus level between 3.5 and 5.5 mg/dL for dialysis patients. Dietary phosphorus should be restricted to 0.8 to 1.0 gram/day. However, even dietary phosphorus restriction is insufficient to adequately control serum phosphorus because each hemodialysis session only removes approximately 800 mg or 2400 mg/week. Thus, even in the patient rigidly adhering to a phosphorus restricted diet (800 mg daily), the weekly dietary phosphorus intake is 5600 mg exceeding the capacity of dialysis to remove phosphate. Consequently, it is important to bind phosphorus in the gut before absorption.

The currently available phosphate binders include calcium-containing phosphate binders such as calcium acetate, sevelamer and lanthanum. Aluminum and magnesium containing phosphate binders are no longer used because of their toxicity. Calcium containing phosphate binders lower serum phosphorus by binding phosphorus in the gut. Calcium acetate is the most widely used calcium containing phosphate binder because it has a similar phosphorus binding capacity as calcium carbonate but contains a lesser calcium burden. By weight calcium carbonate contains 40 percent, while calcium acetate contains 21 percent calcium. The better binding of calcium acetate may be due to its better solubility and it also is less dependent on gastric acidity to be dissolved and activated. The maximal dose of elemental calcium given as a phosphate binder should be limited to 1500 mg daily. In the United States, the commercially available calcium acetate contains 169 mg of elemental calcium. Factors which limit or preclude the use of calcium acetate include hypercalcemia, relatively low PTH values, and probably the presence of vascular calcification.

Table 3. Treatments for hyperparathyroidism

1.	Dietary phosphorus restriction and phosphate binders
2.	Calcium supplementation and high calcium dialysate
3.	Calcitriol or other vitamin D receptor activators
4.	Cinacalcet (calcimimetic)
5.	Parathyroidectomy
6.	Ethanol or calcitriol injection of hyperplastic parathyroid glands

Sevelamer hydrochloride and sevelamer carbonate are nonabsorbable agents that do not contain calcium and are cationic polymers which bind phosphorus through ion exchange. Sevelamer carbonate is the buffered form of sevelamer hydrochloride and does not cause metabolic acidosis. In patients not taking a phosphate binder, the initial dose of sevelamer hydrochloride or carbonate is 800 to 1600 mg three times daily with meals. The initial dosing is based on the serum phosphorus value. Although the data are inconclusive, there may be less progression of vascular calcification with sevelamer versus calcium containing phosphate binders. Also, sevelamer may have the added benefit of reducing LDL cholesterol.

Lanthanum, a rare earth element has also been shown to be an effective phosphorus binding agent. Lanthanum is associated with a lower incidence of hypercalcemia than calcium-containing phosphate binders. Another relative advantage of lanthanum is a lower pill burden. As with other phosphate binders, lanthanum should be taken with meals. It must be chewed completely before swallowing. Crushing the tablets and mixing the crushed tablets in apple sauce might also be acceptable.

As shown in a systematic review, there is no difference in the phosphorus binding capacity of the different binders. However an approach that is solely based on calcium based binders often leads to the development of hypercalcemia. Due to the increased cost, use of sevelamer and lanthanum are often restricted to patients with hypercalcemia, or as an adjunct to a regimen supplying a maximum dose of 1500 mg of elemental calcium from calcium based binders.

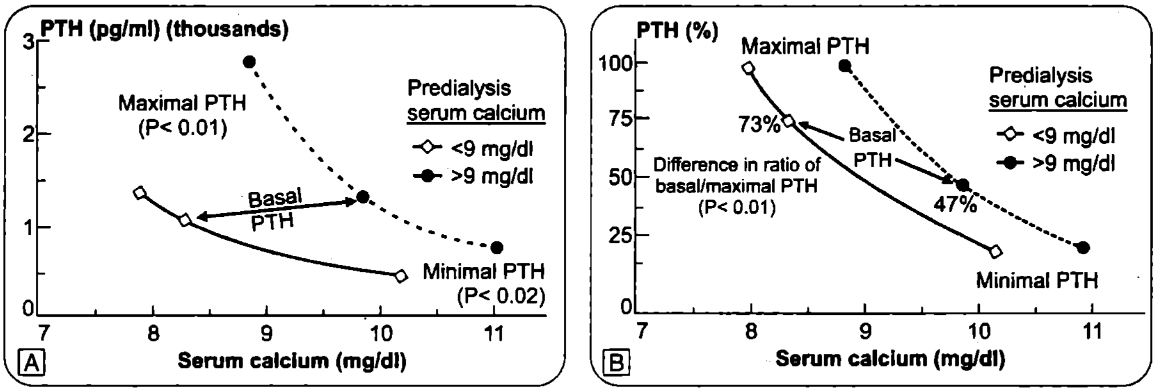
2. *Control of Calcium*

KDOQI recommends maintaining the total calcium level between 8.4 and 9.5 mg/dL. Calcium supplementation may serve to prevent hypocalcemia and suppress PTH secretion. Moreover, the appropriate dialysate calcium is also important. The dialysate calcium concentration should be adjusted according to the serum calcium and PTH level. In hemodialysis patients with hypocalcemia and elevated PTH values, a 3 meq/L or even a 3.5 meq/L dialysate calcium should be used. If the serum calcium is normal or high with a relatively low PTH values, the patient should be dialyzed with dialysate containing 2.5 meq/L of calcium. Conversely, in the patient with hypercalcemia and high PTH levels, it is reasonable to reduce the serum calcium with a low calcium dialysate. But at the same time, it should be appreciated that such an approach might lead to further stimulation of PTH. In summary, the dialysate calcium concentration must be individualized for the needs of the patient.

It has also been found that the predialysis serum calcium concentration affects the dynamics of PTH secretion in dialysis patients (Figs 5A and B). When hypocalcemia was induced with a low calcium dialysate to determine maximal PTH secretion and then hypercalcemia was induced using high calcium dialysate to determine the minimal PTH value, it was shown that even though the basal PTH values were similar in hypocalcemic and normocalcemic dialysis patients, both the maximal PTH and minimal PTH values were less in the hypocalcemic group. The ratio of basal/maximal PTH was greater in the hypocalcemic group. These results suggest that hypocalcemic patients tend to have less severe 2°HPT and also presumably less parathyroid gland mass. Furthermore, the response to calcitriol is likely to be better in hypocalcemic patients due to the correction of hypocalcemia with calcitriol.

3. *Treatment with Vitamin D*

Vitamin D insufficiency (<30 ng/ml) occurs frequently in the general population and has an even higher frequency in CKD patients. It has been shown in several studies that correcting vitamin D level to >30 ng/ml leads to a significant reduction in PTH in patients with stage 3 CKD



Figures 5A and B: Effect of serum calcium concentration on predialysis PTH values in hemodialysis patients with severe hyperparathyroidism. Hemodialysis patients with predialysis PTH values greater than 500 pg/ml were separated into two groups based on their predialysis serum calcium concentration (<9 mg/dL or >9 mg/dL). PTH-calcium curves were performed in all patients to determine the maximal and minimal PTH values; hypocalcemia was induced with a low calcium dialysate (1 meq/L) and hypercalcemia with a high calcium dialysate (4 meq/L). **A.** Even though the predialysis (basal) PTH value was not different between the two groups, the maximal PTH induced by hypocalcemia and the minimal PTH induced by hypercalcemia were both significantly less in the hypocalcemic group. **B.** When the maximal PTH value was changed to 100 percent, and the basal and minimal PTH were shown as a percentage of the maximal PTH, the ratio of basal to maximal PTH indicates the relative degree of PTH stimulation in the basal (predialysis) state. The significantly higher basal to maximal PTH ratio in the hypocalcemic group suggests that hypocalcemia stimulated PTH in the basal state and resulted in similar basal (predialysis) PTH levels in the two groups even though the maximal PTH value in pg/ml was less (see Figure A) in the hypocalcemic group with a trend toward improved PTH level in stage 4 CKD. Despite, the relatively reduced ability of vitamin D to correct PTH levels in stage 4 and 5 CKD patients, attempts should be made to correct the vitamin D insufficiency. This is because, recent data suggest a potential role for 25(OH)-vitamin D in a number of tissues independent of the classical vitamin D pathway in the kidney. The autocrine effects of vitamin D include control of local inflammation and cell cycle regulation. Also, deficiency of vitamin D has been associated with increased cardiovascular disease and mortality in the general population. Vitamin D deficiency may be corrected by the use of either cholecalciferol or ergocalciferol.

In patients with stages 4 and 5 CKD, calcitriol treatment is more effective in reducing PTH levels than 25(OH) vitamin D. Because calcitriol increases the gut absorption of calcium and phosphorus, it should not be started if a patient has hypercalcemia (serum calcium >10.5 mg/dL) or hyperphosphatemia (serum phosphorus >5.5 mg/dL). There have been several studies which have evaluated the route of administration (oral vs intravenous) and the frequency of dosing (daily vs intermittent bolus). In essence, these studies have shown that the route of administration and dosing does not matter with regards to pharmacokinetics, percent PTH suppression and incidence of hypercalcemia and hyperphosphatemia. While intermittent dosing has not been shown to be better than daily dosing, the advantage of intermittent dosing is better compliance because the dose (oral or intravenous) can be administered at each dialysis session. Failure to control serum phosphorus is associated with a decreased response to calcitriol. Finally, for a similarly elevated PTH value, the presence of hypocalcemia portends an increased likelihood of a better response to calcitriol (Figs 5A and B).

Dosing of calcitriol depends on the magnitude of hyperparathyroidism and the serum calcium and phosphorus levels. In normal humans, the daily physiologic production of calcitriol has been estimated to be approximately 1 μg. In dialysis patients, the minimal dose of calcitriol needed for a PTH response is 0.5 μg thrice weekly. A maximal calcitriol dose of 2.0 μg thrice weekly is generally used to treat severe 2°HPT. In patients who respond to calcitriol, the dose of calcitriol often needs to be reduced as PTH values decrease and serum alkaline phosphatase values approach normal. At this stage, hypercalcemia often develops if the initial dose of calcitriol is maintained. Moreover, it should be emphasized that the goal of treatment is not to bring PTH *values into the normal range (10 to 65 pg/ml), but rather to keep PTH value in the 150 to 300 pg/ml range associated* with normal bone remodeling in the dialysis patient.

During calcitriol treatment, the serum phosphorus should be maintained <5.0 mg/dL. This is sometimes difficult because calcitriol enhances intestinal phosphorus absorption and may be associated with decreased bone buffering. Often it is necessary to discontinue or reduce the calcitriol dose because of the failure to control serum phosphorus. To prevent the development of hypercalcemia during calcitriol treatment, it is customary to reduce the dialysate calcium to 2.5 mEq/L. If hypercalcemia develops during calcitriol treatment, discontinuation of calcitriol is required until serum calcium returns to an acceptable value. At that time, calcitriol is restarted at one half the original dose. If during calcitriol treatment PTH values fall to <150 pg/ml, calcitriol should be stopped. If the PTH value again increases to >400 pg/ml, calcitriol should be restarted at 50 percent of the initial dose.

An important consideration with calcitriol therapy is the marked difference in the response to calcitriol. In general, the response to calcitriol is less in dialysis patients with severe 2°HPT (>800 pg/ml) than in patients with moderate hyperparathyroidism (500 to 800 pg/ml). It is likely that resistance to calcitriol therapy is associated with severe parathyroid gland hyperplasia and the presence of nodular hyperplasia which is more common in large parathyroid glands. In nodular hyperplasia, a decreased density of vitamin D receptors has been reported. Calcitriol or its analogues are now often combined with the calcimimetic cinacalcet, to more effectively treat 2°HPT (see below).

4. *Calcitriol Analogues*

Calcitriol and its analogues are collectively called vitamin D receptor activators. Because of the frequent side effects of hypercalcemia and hyperphosphatemia associated with calcitriol treatment, analogues have been developed with a goal to have the same suppressive effect on PTH but with lesser effects on calcium and phosphorus. 22-oxacalcitriol (maxicalcitol) is one analogue which has been developed; it has a shorter plasma half-life than calcitriol but may not have a similar suppressive effect on PTH. Its shorter plasma half-life is due to less binding to vitamin D binding protein. Other vitamin D analogues which are currently commercially available and with more promise, include 19-Nor-1,25 dihydroxyvitamin D_2 (paricalcitol) and 1-alpha hydroxyvitamin D_2 (doxercalciferol). Studies have shown that these two calcitriol analogues may have less calcemic and phosphatemic effects than calcitriol. Observational analyses have shown that treatment with paricalcitol and doxercalciferol enhanced survival in hemodialysis patients. Also, another study showed enhanced survival benefit of paricalcitol as compared to calcitriol. A prospective study confirming these observations has yet to be performed. Also, these clinical studies have shown that all analogues have the potential of increasing calcium and phosphorus levels when used in high doses.

5. Calcium-sensing Receptor Agonist (Calcimimetics)

The most recent treatment modality for 2°HPT is the calcimimetic. Calcimimetics act to directly stimulating the calcium sensing receptor in the presence of calcium. They act at the G protein and mimic the action of extracellular calcium on the calcium receptor of the parathyroid cell. As a result, cytosolic calcium concentration is increased and PTH secretion is inhibited. Cinacalcet, the first calcimimetic to be developed, produces a dose dependent reduction of PTH secretion. Thus, the higher the dose, the longer the duration of PTH suppression. Cinacalcet is started in a dose of 30 mg once daily, and the dose may be uptitrated every two to four weeks till the goal PTH is achieved or a maximum dose of 180 mg/day is given. Studies have shown that the addition of cinacalcet to current treatment regimens increases the percentage of patients who are able to attain KDOQI endpoints related to PTH, calcium and phosphorus levels. However, no prospective trial has clearly shown that the improved biochemical control reduces vascular calcifications and improves cardiovascular outcomes. Nevertheless, cinacalcet has been increasingly used over the past few years, either as a sole agent or frequently together with vitamin D receptor activators for the treatment of 2°HPT. Moreover, cinacalcet will help to correct the hypercalcemia and hyperphosphatemia caused by vitamin D receptor activators in addition to lowering PTH. The most common adverse effects noted with cinacalcet are nausea and vomiting. Also, cinacalcet should not be started if total serum calcium is less than 8.4 mg/dL as it can cause significant hypocalcemia.

In pre-dialysis patients, use of cinacalcet has not yet been adequately studied. It has been noted to cause hypocalcemia more frequently, and also results in mild hyperphosphatemia and an increase in urinary calcium excretion. The latter two effects are seen because of PTH suppression.

6. Parathyroidectomy

There are no exact indications for the performance of parathyroidectomy. Patients with severe 2°HPT who are refractory to treatment with calcitriol and cinacalcet should be seriously considered for parathyroidectomy if an experienced parathyroid surgeon is available. Similarly, in the patient with marked hyperparathyroidism and the inability to control the hyperphosphatemia or hypercalcemia, it would be reasonable to proceed to parathyroidectomy. Others indications for parathyroidectomy include markedly elevated PTH values with calciphylaxis and/or soft tissue calcification. It has also been suggested that the presence of parathyroid glands greater than 1 cm^3 in size in ultrasound studies is a strong indication for parathyroidectomy. In centers with an experienced parathyroid surgeon, it may be reasonable to proceed with parathyroidectomy as a first line approach even before medical therapy, as parathyroidectomy is likely more cost-effective in the long term.

Determining what constitutes refractory hyperparathyroidism may be difficult. The higher the PTH, the lower the likelihood of response to medical therapy. Eighty percent of patients with mild hyperparathyroidism (PTH 300 to 500 pg/ml), 60 percent of patients with moderate hyperparathyroidism (PTH 500 to 800 pg/ml) and only 22 percent of patients with severe hyperparathyroidism (PTH >800 pg/ml) are reported to achieve a PTH level of <300 pg/ml with cinacalcet therapy. Also, parathyroidectomy may be indicated if there are unacceptable adverse effects of medical therapy or poor patient compliance with therapy.

Before a parathyroidectomy is performed, it is important to establish that aluminum toxicity is not present. Both subtotal parathyroidectomy in which a remnant of tissue is left and total parathyroidectomy with autotransplantation of the parathyroid tissue into the brachioradialis muscle in the forearm are performed in dialysis patients with 2°HPT. Approximately 5 to 15 percent of patients have recurrent hyperparathyroidism after parathyroidectomy. Recurrence does not depend on the type of operation, but rather on the proliferative capacity of the remnant tissue. Recurrence is greatest in remnant parathyroid tissue in which nodular hyperplasia is present. Thus, the surgeon must be careful in the selection of parathyroid tissue for transplantation (auto transplantation) or in tissue to be left behind in the neck (subtotal).

7. Ethanol or Calcitriol Injection

Ultrasonographic guided ethanol injection, or more recently calcitriol injection into the largest parathyroid glands has been used to treat hyperparathyroidism refractory to calcitriol therapy. The goal of the procedure is to markedly reduce PTH secretion by injecting ethanol or calcitriol to induce necrosis of the largest parathyroid glands. The large parathyroid glands often demonstrate nodular hyperplasia, rather than diffuse hyperplasia and the nodules not only secrete more PTH than the remaining parathyroids, but also have fewer vitamin D receptors making them more refractory to calcitriol therapy. In most patients, PTH values are reduced after the intraparathyroid injection and they become responsive to calcitriol treatment. This approach to the treatment of refractory hyperparathyroidism has been used in a limited number of dialysis centers in Japan and Europe. In a Japanese study performed in a large number of dialysis patients, it was shown that in skilled hands, this approach might be a viable alternative to parathyroidectomy.

8. Treatment of Aluminum Toxicity

Prevention of aluminum toxicity is critical because of the high morbidity associated with aluminum toxicity. The serum and dialysate water aluminum level must be monitored on a continual basis and long term use of aluminum based phosphate binders should be avoided. Once aluminum bone disease has developed, removal of sources of aluminum such as aluminum-containing phosphate binders and high dialysate aluminum content is mandatory.

In asymptomatic patients with serum aluminum <100 µg/L, treatment of aluminum bone disease is mainly removal of the source of the aluminum and the monitoring of serum and dialysate aluminum levels. DFO treatment is indicated only if serum aluminum is >150 to 200 µg/L, CNS changes (seizure, speech disorder, etc.) are present, or after a DFO challenge test, serum aluminum increases by more than 100 µg/L with the development of CNS symptoms. DFO chelates tissue aluminum and as a result circulating aluminum values increase greatly. DFO treatment is not a benign therapy because it has multiple side effects and thus, when necessary only low doses of DFO, 5 mg/kg, should be used. Side effects of DFO treatment in dialysis patients are many but the most serious concern is infection with mucormycosis (rhizopus species), *Yersinia* and *Salmonella*. These organisms are siderophores and use feroxamine to promote growth. Aluminoxamine and feroxamine are the chelated products of the DFO treatment and normally they are excreted by the kidney but accumulate in patients with renal failure. Other side effects of DFO treatment include: a) hypersensitivity reactions; b) hypotension; c) acute aluminum neurotoxicity (seizure, coma and sudden death) due to marked increases in serum aluminum levels; and d) ophthalmologic complications such as cataracts, acute irreversible visual loss and retinal detachment.

9. Treatment of Beta 2 Amyloidosis

Symptomatic treatment with pain medication is generally required for beta 2 amyloidosis. Surgical intervention for the carpal tunnel syndrome and arthroscopic or open surgery for the removal of amyloid infiltrated synovium in other arthropathies may be necessary and total replacement of diseased joints is also sometimes required. Bone cysts may require curettage and bone grafting. After renal transplantation, plasma beta 2 microglobulin levels return to normal and bone pain resolves quickly even though rapid resolution of amyloid on the articular surface and bone cyst does not occur.

CONCLUSION

Renal osteodystrophy develops in the majority of patients with stage 3 to 5 CKD, and almost universally in CKD stage 5D. The different types of osteodystrophy are osteitis fibrosa, mixed disease, adynamic bone and osteomalacia. Currently osteitis fibrosa is the most common form of renal osteodystrophy. Elevated serum phosphorus levels, hypocalcemia, calcitriol deficiency and metabolic acidosis contribute to the development of 2°HPT in renal failure. FGF-23 is a recently discovered modulator of phosphorus balance, and FGF-23 levels rise even in early stages of CKD. To make a specific diagnosis of renal osteodystrophy, use of noninvasive tests like PTH have lacked sensitivity at PTH values between 150 and 450 pg/ml. The gold standard for making a diagnosis is the bone biopsy, however, it is invasive and processing is only available in a limited number of centers. Studies have shown associations between disorders of mineral metabolism and fractures, vascular calcifications, cardiovascular disease and mortality. It is therefore important to address the mineral abnormalities and osteodystrophy. Treatment options for high bone turnover disease include phosphate binders, vitamin D receptor activators, calcimimetics and parathyroidectomy. Adynamic bone is treated by limiting the use of calcium based binders and using a 2.5 meq/l calcium dialysate. In conclusion, renal osteodystrophy remains a major clinical challenge and its management continues to evolve.

KEY POINTS

- Causes for secondary hyperparathyroidism (2°HPT) include hypocalcemia, phosphate retention, a deficiency of calcitriol, and skeletal resistance to PTH
- Mineral metabolism is altered in progressive CKD by changes in serum calcium, phosphate, PTH, calcitriol and FGF-23
- Reduced ability to excrete phosphate in advanced CKD is a major factor contributing to the development of 2°HPT and renal osteodystrophy
- 2°HPT is the cause of osteitis fibrosa, the most common form of renal osteodystrophy
- Aluminum toxicity in dialysis patients causes "low turnover" osteomalacia, an uncommon form of renal osteodystrophy today
- Adynamic bone, another common form of renal osteodystrophy, is associated with relatively low PTH values, old age, diabetes, CAPD, and high calcium intake/exposure
- The incidence of another form of bone disease in dialysis patient, beta 2-amyloidosis has declined in recent years probably because of better dialyzer clearance of beta 2-amyloid
- Vitamin D receptor activators, cinacalcet (calcimimetic) and parathyroidectomy are the primary treatments for 2°HPT
- Indications for parathyroidectomy are discussed
- The distal (acral) form of calciphylaxis is associated with high PTH values, but the nonPTH mediated proximal form has become increasingly more common.

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An Overview of Leptospirosis: Renal and Hepatic Syndrome

R Kasi Visweswaran

INTRODUCTION

The term leptospirosis is used to denote a zoonotic disease caused by leptospiral group of organisms. The leptospirosis group consists of serogroups or serovars. Infection with various serogroups and serovars gives rise to protean manifestations and has been variously described as Weil's disease, Swineherd's disease, canicola fever, mud fever, autumn fever, field fever, seven-day fever and Fort Bragg fever. Some serovars have greater predilection for producing specific clinical manifestations. It has been noted that serovars icterohaemorrhagiae, hebdomadis, autumnalis and canicola have greater predilection for producing Weil's disease, seven-day fever, autumn fever and aseptic meningitis, respectively. However, it has also been recognized that infection with the same serovar can produce different clinical syndromes and the same clinical syndrome can be produced by different serovars. Hence, the use of the general term of leptospirosis is more appropriate.[1]

Till recently the disease was either overlooked or under-reported mainly due to lack of awareness, varying clinical manifestations, self-limiting nature of milder infections and a non-availability of simple diagnostic tests. More and more cases are reported from all over the world because of increasing awareness and improved diagnostic facilities.

HISTORY

In 1986, Adolf Weil, in Heidelberg, Germany, established leptospiral jaundice as a separate clinical entity from other infectious disease of the liver with juandice.[2] The term Weil's disease was coined by Goldschmidt in 1987.[3] In 1907, Hunter pointed out the commonly encountered clinical features, particularly, severe muscular pain, bleeding tendency and renal failure. In 1914, Inada et al.[4] At the Imperial University of Kyushu, Japan, saw the leptospiral organisms in the liver of the guinea pig which had been injected with the serum of patient suffering from Weil's disease. Thus this organism was named *Leptospira* icterohaemorrhagiae. The term Weil's disease was used to describe a syndrome of severe leptospirosis, characterized by abrupt onset of a febrile illness associated with severe muscular pain, deep jaundice, hemorrhagic tendency, particularly subconjunctival hemorrhage and acute renal failure. Stimson[5] described a spirochete in the shape of question mark in the kidney tissue of a patient who died of presumed yellow fever and named it *Spirochete interrogans.* The sections and photographs were restudied in 1940 by Sillards, and ultimately the name *Leptospira interrogans* was accepted.[6]

MICROBIOLOGY AND TAXONOMY

Leptospiras are about 1 micron thick, motile aerobic organisms of length varying from 6-20 microns and belong to the family Spirochete. They have hooked ends resembling a questions mark and, hence, the name interrogans. *L. interrogans* is the one and the only species in the genus leptospira. The species *Leptospira interrogans* is divided in to two complexes-*interrogans* and *biflexa* (the former pathogenic and the later is sapirophytic). The complex *L. interrogans* is broadly subdivided into 19 serogroups, e.g. icterohaemorrhagiae, hebdomadis, autumnalis, canicola, pomona, australis, grippotyphosa, etc. Each of these serogroups has common antigenic properties among themselves. These serogroups are further subdivided into serovars based on certain antigenic differences. There are about 180 serovars identified so far.[1] Hence, the correct current taxonomy for icterohaemorrhagiae serovar of L. icterohaemorrhagiae, is *L. interrogans* serogroup icterohaemorrhagiae serovars and not "*L. icterohaemorrhagiae*".

The spirochetal organism is so tightly coiled that the coils can be identified only by dark ground illumination or phase contrast microscopy in the living state and by electron microscopy in the specimens. They are actively motile organisms and do not take bacterial stains. The structure of the leptospira have been more clearly understood. It consists of an outer envelope (OE), periplasmic space, cell wall, cell contents and flagella. The OE contains lipopolysaccharides, which have the pyrogenic and cytotoxic properties which are mediated through release of IL8, TNFα, IL-1 and IL-6 from endothelial cells. The glucolipoprotein in the organism is a heat stable toxin and capable of inhibiting Na-K-ATPase in renal tubules. The peptidoglycans estimate phagocytosis and produce TNFα from monocytes. The cell wall synthesizing enzymes involved in peptidoglycan biosynthesis are the penicillin binding protein and are essential for cell generation and survival. Thus understanding the structure has helped to explain the protean clinical manifestations of infections. They may be stained by Giemsa stain or by silver impregnation methods. Leptospira are very delicate organisms; they are killed by exposure to heat at 50°C for 10 minutes, exposure to direct sunlight or dry surroundings. The organisms are rapidly destroyed by exposure to gastric juice, bile, antiseptics or disinfectants.

They can be grown in media enriched with rabbit's serum. Fletcher's media or Stuart's media can be used to grow the organisms. The organisms may survive in oxalated blood for upto 11 days. If the material for culture is inoculated intraperitoneally into a guinea pig, the leptospira invade the blood stream more rapidly than other bacteria, and thus, culture of heart blood within 10-15 minutes gives a culture free of other bacterial contaminants. Such samples can be grown in chorioallantoic membrane of chick embryos.

EPIDEMIOLOGY

Leptospirosis is one of the widespread zoonosis in the world. It has been reported from almost all countries, especially in the tropical climate. It is not seen in regions of extremely cold climate like Antarctica. It has been reported from various parts of India. On average, over 100 patients presenting with the typical features of Weil's syndrome are seen in all major hospitals in Kerala and in Southwestern part of India annually for the last decade. The disease has been extensively reported from other areas of peninsular Southeast Asia, South America and African countries.

Infection may occur in several domestic or wild animals. Rats are the common carriers of the most pathogenic strains. Other animals like field mice, hedgehogs, pigs and dogs also act as carriers. The manifestations in the infected animals may vary from indolent carrier state to a fatal illness. The organisms are known to survive in the proximal convoluted tubules of the reservoir host and are shed in the urine for months or even years. Thus, the pathogenic strain propagates itself. The infected urine of the reservoir animals may contain up to 100 million leptospirosis per milliliter. In stagnant water, sewage or drains, which are not exposed to direct sunlight, the organisms may survive for weeks. A neutral or slightly alkaline pH with low salinity is more favorable for the organisms. The organisms do not survive long if the water is contaminated with other microorganisms or detergents.

The infection in humans is accidental and is not a part of the life cycle of the organism. The infection occurs when humans come into contact with infected animal tissue, fluids or contaminated water. The organisms gain access through small cuts or abrasions in skin or mucous membrane. There is also a possibility of entry of the organisms through intact mucous membrane. Working in sewers, agricultural workers, butchers, fish cleaners or people who take baths in contaminated water, occupational exposure may not be invariably seen. Observations in our hospital show that 80 percent of patients are agricultural workers or those who have chances of coming into contact with the infected environment.

Leptospirosis occurs in both sexes and in all age groups. It has also been reported in children. We noted a male preponderance of 7:1 mostly because the heavy manual and outdoor activity is undertaken by the male population in this part of the world. The peak incidence is seen in the age group of 11-40 years. The male preponderance and increased incidence in the age group of 11-40 years have been observed in the studies from other parts of the world. In the United States, the disease occurs more during the hot season from July to October. It has been observed that there is a sharp increase in the incidence of leptospirosis in parts of Southern India during the rainy season from June to November or following flooding and overflowing drains during rainy season.

PATHOLOGY

The gross pathology of patients dying of severe leptospirosis includes widespread petechial or ecchymotic hemorrhages in the skin, mucosa, serosa, heart, lungs, liver, spleen, kidneys, adrenals, skeletal muscle and stomach. The liver and kidneys are slightly enlarged. Lungs are often heavy and edematous. Splenic enlargement is not prominent. Significant bile staining is also seen in the tissues of jaundiced patients. Microscopy of the liver shows nonspecific changes and include cloudy swelling of parenchymal cells, disruption of cords, enlargement of Kupffer cells and bile stasis in the central part of hepatic lobule. Leptospiral organisms are often not demonstrated in the liver and morphologic changes do not correlate with severity of the disease.

In the kidneys, the striking abnormalities are noted by microscopy. The glomeruli are essentially normal or may show nonspecific mesangial reactions. Changes in the proximal tubules include degeneration, necrosis and disruption of basement membrane. The distal tubules may be dilated and contain bile stained casts. Special stains and silver impregnation technique may reveal the presence of the organisms in the tubule cells and lumen. It has been noted that leptospira can be identified in the tissue by special stains only in the proximal convoluted tubules. As the disease progresses, antibodies may appear and cellular infiltration may be seen in the tubules and interstitium.

Focal areas of degeneration of individual muscle fibrils and loss of architecture associated with inflammation in the skeletal muscle are considered specific for leptospirosis. Leptospira antigens have been demonstrated in these lesions by fluorescent antibody technique. The above changes may also be found in the myocardium. Myocarditis may be an important cause of hypotension and death in these patients. In patients who survive; healing of the affected muscle occurs through formation of new fibrils. Pulmonary changes include patchy, localized, hemorrhagic pneumonitis. Bile staining of leptomeninges and choroids plexus may be seen, but there are no microscopic changes.

PATHOGENESIS

The kidneys are greatly vulnerable to the effect of drugs, toxins, and other agents due to many factors. The high blood flow per gram of tissue is exaggerated in the renal cortex which receives 90 percent of the renal blood flow. The high metabolic activity and oxygen consumption of the proximal tubule cells make the kidney prone to anoxic injury. The large endothelial vascular surface area predisposes to damage by endothelial toxins. The other important factors include transcellular transport, luminal concentration of solutes, drugs and toxins due to countercurrent multiplier system, uncoupling of toxin protein complexes and release of toxins. In leptospirosis, many of these factors may be operating. The high blood flow rate per gram of renal tissue predisposes the kidney to handle a greater load of organisms in the leptospiremic phase. Renal ischemia, toxin, bacterial migration and immunologic reaction may be responsible for the renal damage. The large endothelial surface area in the kidney is also exposed to the vasculotoxins, which may be produced by leptospira. The central lesion characteristics of all forms of leptospirosis is capillary endothelial damage, leading to extravascular cells and fluids.

When pathogenic strain of leptospira enters a susceptible (non-immune) host, the nonspecific factors like complement, lysozyme or IgM which can effectively eliminate the nonpathogenic strains are ineffective. The organisms multiply in the blood and cerebrospinal fluid (CSF) leading to leptospiremia. Extensive capillary endothelial damage occurs leading to extravasation of cells and fluid. Since they are not pyogenic, acute inflammatory response does not occur.

Based on clinical and experimental studies the following mechanism and sequence of events have been postulated. The passage of the leptospira through the glomerular capillary bed leads to capillary damage and initiates the nonspecific glomerular changes like mesangial proliferations. The leptospiral glycolipoproteins are considered to be responsible for the damage and initiates the nonspecific glomerular changes like mesangial proliferation. Virulent leptospira adhere to renal epithelial cells. The leptospiral glycolipoprotein also inhibits Na-K-ATPase in the renal tubules. This may occur in the patients with acute renal failure. The invasion of the proximal tubule cells occurs because of the migration of the leptospira from the peritubular capillary through the interstitium to the tubule cell and later into the tubular lumen. The leptospiral lipopolysaccharide (LPS) may promote platelets aggregation leading to coagulation and/or bleeding. The LPS also stimulates the immune system to produce antibodies. LPS can activate macrophages and B cells. A combination of bacterial enzymes, metabolites, exotoxins, complement mediated damage, or vasculotoxicity may be responsible for the renal tubular damage and development of acute renal failure. In addition to the direct nephrotoxic damage, nonspecific effects of systemic infections with resulting hypovolemia, and myoglobinuria from extensive muscle damage may be important contributory factors. Decreased fluid intake, increased insensible fluid loss, increased vascular permeability may contribute to the hypovolemia and hypotension. Definite increase in blood viscosity has been noted and may be related to increase in fibrinogen which in turn may be caused by severe tissue and endothelial damage. Experiments to demonstrate exotoxins in the pathogenesis of leptospirosis have not been successful. Presence of leptospira in the renal tissue is essential for the development of renal lesions and killed leptospira failed to provoke any structural lesion in guinea pigs.

CLINICAL FEATURES

The clinical manifestations of leptospirosis occur between 7-14 days of the actual entry of the organisms into the body. The incubation period may vary from 2 to 20 days. The length of the incubation period does not seem to have any prognostic significance. The severity of the disease may vary from subclinical form to single or multiple organs involvement or failure. Inapparent infection with positive serology may be seen in 25-50 percent of workers at high-risk. Severe cases of multi-organ failure is associated with a very high mortality.

The initial phase of the leptospiral illness is characterized by leptospiremia. The organisms are found in the blood and CSF. The onset is usually abrupt and associated with fever and chills. Severe headache and muscular pain occur in most patients. Muscles of the thigh and back are usually tender to touch and there may be cutaneous hyperparesthesia. Other manifestations in this phase include anorexia, nausea, vomiting, diarrhea, cough, chest pain, disturbed sensorium, maculopapular skin rash and conjunctival suffusion. Splenomegaly and lymphadenopathy may occur in small number of cases. The leptospiremic phase subsides in 4-9 days when the fever may remit. Very unusual manifestations reported during this stage include arthritis, parotitis, epididymitis, testicular pain and pancreatitis.

The second phase or the immune phase of the illness is the more critical period in the illness. During this phase fever may be absent or mild. Jaundice and hemorrhagic tendency become marked. Persistent vomiting, bruises in the skin or internal hemorrhage may occur. The subconjunctival hemorrhage often occurs early in the stage of illness. Other hemorrhagic manifestations include epistaxis, hemoptysis, gastrointestinal, adrenal or intracranial hemorrhage. These have been explained on the basis of capillary injury due to vasculitis.

Abnormalities of cardiac conduction have been described in some cases. These include proxysmal atrial fibrillation, atrial flutter, ventricular tachycardia or ventricular premature contractions. Intractable hypotension may be seen.

Another important event that occurs during this stage is the development of acute renal failure characterized by steady increase of blood urea nitrogen and serum creatinine. The blood pressure may be normal, but hypotension is not infrequent. Patients who are normotensive often show steady elevations of blood urea nitrogen and serum creatinine in the presence of a normal or increased urinary output. The diagnosis of acute renal failure may be delayed in such cases. Nearly 50 percent of the patients have been noted to have abnormalities in urinary concentration. Patients may deteriorate from a state of confusion to stupor and coma. The hypotension may be profound and fluid may be necessary to replace the ECF volume. After adequate fluid replacement, if the blood pressure is still low, dopamine infusion may be commenced. Those with hypotension and hypoalbuminemia will need colloids in the form of plasma, or plasma volume expanders (Hydroxyethyl starch). In patients who have hypotension with normal CVP, steroid therapy may help. These patients may go into diuretic phase, which may be profound and may last longer than the other cases of acute renal failure. The jaundice, anorexia, and bleeding tendency also improve rapidly. The hepatic involvement may vary from anicteric hepatitis to severe hapatocellular failure. The level of serum bilirubin in severe cases may be over 50 mg percent.

Some patients may go through an illness closely resembling meningitis. In the meningitic form of the disease, the patient may have some other manifestations of Weil's syndrome like myalgia, subconjunctival hemorrhage, jaundice and renal failure in addition to clinical features or meningitis associated with increased CSF protein and lymphocytes. Clinically, it may be difficult to diagnose the meningitic form, unless it is accompanied by other manifestations like hemorrhage, jaundice, myalgia or renal failure. Leptospirosis has also been reported to produce cerebral arteritis and polyradiculoneuritis. In children, hypertension, acalculous cholecystitis and vasculitis producing gangrene have been seen.

Pulmonary involvement with development of hypoxia and adult respiratory distress syndrome (ARDS) has been observed.

Hemorrhagic pulmonitis and pulmonary capillary leak has been documented in leptospirosis. In view of the poor prognosis of those who remain hypoxic, early ventilatory support combined with extracorporeal membrane oxygenation may be attempted to bring the mortality rate down.

An illness characterized by the development of bilateral, symmetrical, raised, erythematous rash over the pretibial area associated with splenomegaly and other symptoms of the leptospiremic phase was shown to be due to outbreak of infection with autumnalis sero group. This outbreak occurred in Fort Bragg in 1942 and is known as Fort Bragg fever (pretibial fever). Other serogroups have also been implicated in the development of pretibial fever.

Diagnosis

As in other infectious diseases, patients suffering from leptospirosis may show all or only a few of the clinical manifestations. The manifestations may vary with the serotype of the infecting leptospira. Because of varied clinical manifestations, a high index of suspicion is necessary to diagnose leptospirosis. Diagnosis must be made on the basis of clinical manifestations, urinalysis, blood counts, liver and renal function tests and demonstration of the organism and serology.

URINALYSIS

The urine may be deep colored depending on the degree of jaundice urinary volume may be normal or reduced. Bilirubin, urobilinogen and protein may be detected in the urine. In severe cases, the urinary sediment may be loaded with bile pigments. Various types of bile stained casts. These may be seen in the centrifuged deposit.

BLOOD COUNTS

The presence of polymorphonuclear leukocytosis with WBC counts in the region of 20,000-30,000 may help to differentiate the jaundice of leptospirosis from viral hepatitis. Even in the presence of bleeding tendency, the coagulation profile may be normal signifying capillary wall damage as the source of generalized bleeding tendency. The erythrocyte sedimentation rate is increased and the degree of anemia correlates with the extent of blood loss.

LIVER FUNCTION TESTS

In jaundiced patients, there is a predominantly conjugated hyperbilirubinemia. The serum bilirubin may be very high, reaching levels of 40-60 mg/dl. Although the serum bilirubin levels are very high liver enzymes such as ALT, alkaline phosphatase may be only mildly elevated. The serum albumin has been suggested as a marker of poor prognosis. The prothrombin time may be prolonged. Creatinine phosphokinase has been found to be elevated in nearly 30 percent of the cases.

RENAL FUNCTION TESTS

Cases with renal failure have markedly elevated levels of blood urea nitrogen and serum creatinine. Alston and Broom in their study at a time when dialysis was not freely available found that the mortality correlated closely with the level of blood urea. However, with the advent of dialysis, even patients who have high level of blood urea and serum creatinine, can be saved. Nearly 50 percent of the patients may have nonoliguric acute renal failure, and this may be responsible for the delayed detection of renal involvement in many cases. The serum potassium tends to be elevated particularly in patients with renal failure. There may be mild degree of metabolic acidosis.

CSF STUDIES

The CSF studies in patients who present with the meningitic form of leptospirosis may show a picture indistinguishable from nontuberculous lymphocytic meningitis with normal glucose, slightly elevated protein and presence of mononuclear cells.

OTHER INVESTIGATIONS

The electrocardiogram may be abnormal in about 30 percent cases. Sinus tachycardia is the most common finding. About 6-10 percent of cases may have other abnormalities like atrial fibrillation, supraventricular ectopics or other nonspecific changes.

The proof of infection by leptospiral organism comes from the demonstration of the organism in the body fluids by growing the organism in culture, or by demonstration of specific antibodies in the serum. The organism can be demonstrated in the blood during the leptospiremic phase of the illness. Five milliliters of blood is collected in a tube containing anticoagulant and centrifuged at 500 rpm for 10 minutes. The supernatant plasma is removed and centrifuged again at 3000 rpm for 30 minutes. The supernatant is discarded and the deposit is examined under the dark-field microscope for the organisms which appear as thin coils with hooked end and demonstrate spinning or gliding movement. The delay between the collections and examination, use of drugs before sampling and the delicate nature of the organism account for the relatively low yield of positivity by these tests.

From the second week, the organisms can be demonstrated in alkaline urine. It is necessary to administer alkalies to the patient for a few hours before collection of the urine specimen, because the leptospira cannot survive in the acidic urine. Although leptospiral organisms may be present in the CSF by early 2nd week, their detection is very difficult. The organisms may be detected in autopsied kidney, liver and spleen when these organs are stained with silver impregnation methods. Fluorescent antibody techniques may also be used to detect leptospira in urine and tissue preparation. For demonstration of live organisms in body fluids, the specimens must reach the laboratory within minutes of collection and examination must be done without any delay. Fletcher's semisolid medium and Stuart's medium are the culture media generally recommended. The blood cultures must be taken early and before starting chemotherapy. The growth of the organisms in culture takes a long time and may not be relevant from the treatment point of view. The primary culture is incubated at 37°C and samples from culture examined by darkfield microscopy every 3 days. It may take up to 4 weeks for the organisms to grow in the primary culture. When growth is detected, incubation at 28-32°C further promotes the growth of colonies.

SEROLOGICAL METHODS

The patient's serum shows antibodies from the second week of illness. It is advisable to take the first sample or paired sera at the earliest opportunity so that a rise in titre can be observed. A single titre of 1/400 or a four fold rise in titre may be taken as significant. The macroscopic agglutination test or slide test can be used to screen the sera for infection. The formalinized antigen or various serotypes are used and the result noted by the degree of agglutination. This test is, however, not specific. Indirect hemagglutinin test and complement fixation tests are also available.

The "benchmark" procedure used to serologic diagnosis is the microscopic agglutination test. This test is complex and requires the maintenance of culture of live leptospira. The live cultures are used as antigen and tested with serum of patients and agglutination is observed under dark-field microscopy. This test is also partially sero group specific. The complement fixation test is used as a screening test. It gives an idea about the recent infection. As almost all serovars are sensitive to penicillin, microscopic agglutination test is not essential for deciding chemotherapy of these cases or for clinical purposes. Enzyme linked immunosorbent assay (ELISA) test also requires a maintenance of live leptospiral cultures and may lack sensitivity and specificity.

Recently, DNA based techniques are being developed as alternative methods for diagnosis. Restriction endonuclease analysis, hybridization, polymerase chain reaction, random amplified polymorphic DNA finger printing and arbitrarily primed PCR assay have been used in the diagnosis of leptospirosis. PCR is an important molecular tool which may be able to detect as few as 5-10 leptospira per ml of sample. Using this, leptospiral DNA has been detected in aqueous lumen of patient from unilateral uveitis. Although expensive, PCR assay could be used for rapid sensitive and specific detection of leptospiral infection.

DIFFERENTIAL DIAGNOSIS

When typical signs and symptoms of Weil's disease are present, the diagnosis of leptospirosis is generally straightforward. However, leptospirosis may present in other forms and mimic conditions like acute febrile illness, acute viral hepatitis, septicemia with jaundice, malaria, blood dyscrasias, meningitis, coma, hemorrhagic fever with renal syndrome, scrub typhus or Hanta virus infection.

If "influenza" worsens with development of jaundice or renal failure, leptospirosis must be ruled out. Normal or low WBC count accompanied by marked elevation of liver enzymes and jaundice favors viral hepatitis and tends to rule out leptospirosis. Septicemia, blood dyscrasias and malaria can be diagnosed by careful examination of the blood. The CSF studies suggestive of lymphocytic meningitis, together with jaundice, will help to rule out other cerebrospinal, it may be confused with Hanta virus infection. In places like Korea where both Hanta virus infection and leptospirosis are common, blood samples are often taken simultaneously for Hanta virus and leptospira serology. In children, the clinical presentation may resemble mucocutaneous lymph node syndrome (Kawasaki's syndrome).

PREVENTION

Prevention of illness in humans is a matter of simple hygiene, good housekeeping in the work place combined with education of workers. In the Aberdeen fish market, where the incidence was high, things have improved following use of vigorous anti-rat measures and use of disinfectants to clean the areas of possible infection. Early treatment of skin abrasions, provision of protective clothing for workers at risk and avoiding immersion in canals and ponds will go a long way in prevention of the illness in humans. It is possible to administer polyvalent depot vaccine against the common types of leptospira with demonstrable increase in antibody titre. Such measures are not practical on a large scale, particularly since simple hygienic steps and eradication of rats and other animal carriers are more effective.

MANAGEMENT

The main emphasis in the management of leptospirosis must be placed on symptomatic measures. Analgesics, antipyretics and sedatives may be used to alleviate the pain and discomfort of the patient. Some patients may have dehydration and appropriate fluid and electrolyte replacement is warranted. Patients with acute renal failure do well with dialysis. It is necessary to serially monitor the blood urea nitrogen and serum creatinine for early diagnosis of acute renal failure. The bleeding tendency and myocarditis with hypotension may contribute greatly to the mortality and require appropriate management. The use of dopamine to increase the blood pressure may be successful in some patients.

There is considerable controversy regarding the choice of antibiotic. Leptospirosis is a self-limiting illness and mild cases recover uneventfully. Subclinical and undetected cases do not receive any antibiotic. It has been suggested that unless antibiotics are started very early in the leptospiremic phase, they do not alter the clinical course of jaundice, acute renal failure or cerebral hemorrhage. Although there are some justifications for withholding antibiotics, most patients of leptospirosis do receive antibiotic chemotherapy for few days with apparent benefit. As the disease is due to a microorganism, and penicillin effectively clears the blood of the organism, it is justifiable to start a course of benzyl penicillin in doses of 1.2 gm every 6 hours intravenously, or benzathine penicillin 600,000 units intramuscularly twice daily for 7-10 days. Rarely, a Jarisch Herxheimer reaction may occur. Patients who are allergic to penicillin may be given tetracycline 500 mg every 6 hours. If tetracyclines are contraindicated as in children or those in acute renal failure, streptomycin or erythromycin may be used. Since penicillin is uniformly successful in eradicating the infection, the nephrotoxic antibiotics should be avoided.

PROGNOSIS

Most of the patients with mild forms or with single organ involvement recover. In the pre-dialysis era, acute renal failure was an important cause of death. However, with the availability of dialysis in most parts of the world, the mortality due to acute renal failure has declined. Hypotension due to myocarditis and internal hemorrhage continues to be important cause of death in the small percentage of patients. Iridocyclitis may persist for a long time. The outcome of pregnancy in women with severe leptospirosis may be unfavorable. However, the recovery from hepatic and acute renal failure is virtually complete.

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Drug Dosing in Renal Disease

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BACKGROUND

Drugs that are excreted partly or entirely by the kidneys can accumulate when kidney function is reduced. Therefore, these drugs administered for a prolonged period of time can accumulate in renal failure patients and cause toxic side effects. For example, the elimination of aminoglycosides can be 25 to 50 times slower in uremic patients. In addition, drugs metabolized by the liver produce polar metabolites that are excreted by the kidney. These metabolites accumulate in patients with renal failure often leading to adverse drug reactions. Therapeutic drug monitoring of all renally eliminated drugs is not feasible. Changes in drug absorption, distribution, metabolism and excretion must also be considered in the therapeutic management of patients with renal failure.

In this chapter, general guidelines for appropriate dosage adjustment of medications for patients with impaired renal function will be presented. Furthermore, drug dosing for the dialysis and hemofiltration therapies will be discussed. Basic principles of estimating renal function and a summary of drug pharmacokinetics, pharmacodynamics, interactions and toxicities are presented. The recommendations presented are only "initial dosing" guidelines for the typical 70 kilogram (kg) person and should be used with caution, as drug dosing is influenced by increased or decreased weight, body composition, disease state, age and other factors. Basic knowledge of pharmacokinetic principles aid in the appropriate drug dosing of renally impaired patients. The primary goal in patients with renal disease is to maintain therapeutic concentrations of drugs at an equivalent level to patients with normal renal function.

ESTIMATION OF GLOMERULAR FILTRATION RATE

The decision to adjust the dose of a given drug in a patient with renal failure depends on the level of kidney function and the extent of renal elimination of the drug. The primary measure of renal function is glomerular filtration rate (GFR). For the purpose of drug dosing, GFR is approximately equivalent to creatinine clearance. Therefore, it is necessary to measure creatinine clearance to appropriately adjust drug dosage. Several formulas are used to estimate creatinine clearance. The most commonly used is the Cockcroft-Gault equation:

$$\text{CrCl (ml/min)} = \frac{\begin{array}{c}[(140\text{-age (yrs)}) \times \text{ideal body weight (kg)}] \\ (\text{x } 0.85 \text{ if female})\end{array}}{\text{SCr (mg/dL)} \times 72}$$

Where CrCl is creatinine clearance in ml/minute and SCr is the serum creatinine in mg/dL. The ideal body weight (IBW) should be used if a patient is within 120 percent of their IBW. The IBW is calculated as 50 kg plus 2.3 kg for each inch in height over 5 feet (for men) or 45.5 kg plus 2.3 kg for each inch in height over 5 feet (for women). A patient's actual body weight should be used if the patient weighs less than his IBW. For obese patients, an adjusted body weight calculation should be used. This is calculated as IBW + (0.4 x (Actual BW - IBW). This method of calculating CrCl is accurate only when renal function is stable. When GFR is changing, estimation of CrCl can be very erroneous. Also, the estimation of

CrCl in severe renal failure by the above method can be inaccurate. As GFR declines, a larger percentage of creatinine is secreted rather than filtered; the CrCl calculated by the equation above would overestimate the actual GFR. Although the 24-hour creatinine clearance is also of limited value in this setting, it may give a more accurate estimate of GFR. The 24-hour creatinine clearance is calculated from the following equation:

$$\text{CrCl (ml/min)} = \frac{U \times V}{P}$$

U = Urinary creatinine from 24-hour collection (mg/dL)
V = Volume of urine in ml/min from 24-hour collection (24 hour = 1440 minute)
P = Plasma creatinine (mg/dL)

Unfortunately, dosage adjustment is not as simple as a reduction in dose proportional to the reduction in GFR, since a 24-hour CrCl will also overestimate GFR (increased urinary creatinine due to hypersecretion will increase the numerator of the above equation). Drug accumulation is further affected by the effect of renal disease on the pharmacokinetic properties of each individual drug in a patient.

PHARMACOKINETIC TERMS

Drugs are eliminated from the body via two major pathways: hepatic metabolism and renal elimination. Many drugs metabolized by the liver are converted to active or toxic metabolites that are subsequently eliminated by the kidney. Thus, the kidneys are involved even if a drug is eliminated primarily by liver metabolism. Drugs that are excreted unchanged in the urine are freely filtered through the glomeruli, actively secreted, or reabsorbed by the tubules or eliminated by a combination of these processes. Each process is affected to a different extent in various types of renal diseases. In addition, a few drugs such as insulin and imipenem are metabolized by the enzyme systems located in the kidney.

Although renal failure has the potential to influence all aspects of drug pharmacokinetics and pharmacodynamics, there are specific parameters that affect drug disposition. These include:

- Bioavailability
- Volume of distribution
- Protein binding coefficient
- Elimination coefficient and half-life
- Metabolism

BIOAVAILABILITY

Drug bioavailability is defined as the rate at which a drug enters the central circulation. Intravenously administered drugs enter the venous circulation directly and have the most rapid onset of action. The bioavailability of orally administered drugs is dependent on the absorption of the drug. Absorption of oral agents depends on pH, gastric motility and first pass metabolism by the liver. The oral drug is absorbed directly into the portal circulation and must immediately pass through the liver where extensive metabolism can occur. For example, propranolol is metabolized by more than 90 percent by the first pass effect through the liver. Absorption is also affected by gastrointestinal symptoms, such as vomiting, diarrhea, and edema of the gut. These symptoms are commonly present in renal patients and may prevent or delay oral absorption of many drugs.

Gastric pH is a factor that directly influences oral absorption of drugs. For example, with rising BUN secondary to impaired renal function, gastric pH is increased. This is due to enhanced ammonia production from gastric urease. An increase in pH may hinder the absorption of many drugs. **For example, an acidic environment is required for the conversion of ferrous iron to ferric iron, the form necessary for absorption. Thus, patients with renal insufficiency and increased gastric pH may have impaired ability to absorb iron.** Agents like aluminum hydroxide, calcium acetate, calcium carbonate and sucralfate can both increase the pH of the stomach and bind to certain drugs like ciprofloxacin, ketoconazole and tetracyclines, thereby delaying absorption of these agents. Therefore, administration of these agents should be separated by at least two hours to prevent their malabsorption. Additionally, it has been shown that the absorption of a simple sugar, D-xylose, is delayed in renal patients, suggesting that carbohydrate absorption may generally be impaired.

Concomitantly administered drugs can also compromise drug absorption. Lipid lowering agents such as cholestyramine and colestipol can bind levothyroxine, digoxin, warfarin and phenytoin, significantly reducing their therapeutic efficacy. Finally, the administration of enteral nutrition supplements can also decrease the bioavailability of drugs such as phenytoin.

VOLUME OF DISTRIBUTION

Apparent volume of distribution (VD) is defined as the amount of drug distributed throughout the body divided by plasma concentration of drug at equilibrium. This is not an anatomic space, but a mathematical concept designed to define a therapeutic drug concentration. VD is dependent on specific drug properties such as lipid and water solubility, tissue and protein binding, as well as patient size and composition; these relationships are not linear. Water soluble drugs (aminoglycosides), or highly protein bound drugs (phenytoin), which are restricted to the extracellular fluid space, have a small VD. In contrast, drugs that are lipid soluble (cyclosporine) or widely tissue bound (digoxin), exhibit large VD values. Edema and ascites tend to increase VD of water soluble drugs, whereas dehydration decreases it. Renal insufficiency alters the VD of many drugs, resulting in higher or lower plasma concentrations.

A clinically significant example of the impact of altered VD is digoxin. The VD of digoxin is decreased in renal failure to 230 to 280 liters as compared to the normal VD of 510 liters. As a result of its decreased VD, lower loading doses must be used to avoid toxicity. Another significant example involves aminoglycosides. These agents are water soluble, distributed in the extracellular space and have a very low VD. If the VD is increased, the total serum concentration may appear lower even though the half-life of these drugs may be prolonged. This results in the need for a higher dose given less frequently. The extracorporeal removal of aminoglycosides then becomes a function of the time on dialysis and the rate and extent of equilibration and redistribution of the drug postdialysis. The increase or decrease of VD in renal disease is presented for some commonly used drugs in Table 1.

Table 1. Effect of ESRD on volume of distribution

Increased			*Decreased*
Amikacin	Cloxacillin	Naproxen	Chloramphenicol
Cefazolin	Dicloxacillin	Phenytoin	Digoxin
Cefonicid	Erythromycin	Sulfamethoxazole	Ethambutol
Cefoxitin	Furosemide	Trimethoprim	Methicillin
Cefuroxime	Isoniazid	Vancomycin	Pindolol

PROTEIN BINDING

Many drugs used in renal failure patients are reversibly bound to plasma or tissue proteins. Proteins act as a reservoir or a storage site for these drugs. Generally, the unbound or free drug is responsible for the pharmacologic action of the drug. The portion of the drug that is bound to protein is pharmacologically inactive. Acidic drugs like warfarin, valproic acid, phenytoin and cefazolin are bound to albumin and basic drugs like lidocaine, propranolol and disopyramide are bound to alpha-acid glycoprotein in the serum. Other drugs like cyclosporine are bound to lipoproteins in the serum. The protein binding of acidic drugs is generally decreased in uremia, whereas basic drugs, for the most part, are not affected. Examples of some of these drugs are included in Table 2.

The binding of drugs to serum proteins is influenced by the number of available sites on the protein, the affinity of the drug for the protein, and the potential displacement and/or inhibition of binding by endogenous acidic inhibitors, which accumulate in renal disease. When a drug is displaced from its binding site, it may produce a pharmacologic effect, be distributed to other tissue sites or metabolized. Examples of drugs that are highly protein bound include:

Phenytoin (90%)
Tolbutamide (99%)
Warfarin (99%)
Cefazolin(85%)
Cyclosporine (>90%)

Any drug or disease state that decreases protein binding can result in an increased therapeutic effect. In the case of phenytoin, the total "therapeutic" range in normal individuals is 10 to 20 mg/L. Since 90 percent of the drug is protein bound, the percentage of drug available for pharmacologic action (the free fraction) is 10 percent. This results in a therapeutic level of 1 to 2 mg/L for free fraction of drug. In ESRD patients, the free fraction of phenytoin is increased to 20 percent as a result of drug displacement and lower albumin levels. This causes an increased VD of phenytoin leading to lower serum levels. While a total serum concentration of 5 to 10 mg/L might first appear to be subtherapeutic (since the normal range is 10 to 20 mg/L), after considering the decreased protein binding in renal patients, the free concentration remains within the therapeutic range (20 percent [free fraction]of 5 to 10 mg/L is 1 to 2 mg/L).

Table 2. List of commonly prescribed acidic and basic drugs

Acidic Drugs			*Basic Drugs*	
Cefazolin	Diflunisal	Sulfamethoxazole	Amphotericin B	Fluoxetine
Cefoxitin	Doxycycline	Valproic acid	Clonazepam	Ketoconazole
Ceftriaxone	Methotrexate	Warfarin	Clonidine	Morphine
Cloxacillin	Pentobarbital		Clorazepate	Prazosin
Diazoxide	Phenytoin		Disopyramide	Propafenone
Dicloxacillin	Salicylate			

ELIMINATION COEFFICIENT AND HALF-LIFE

The elimination coefficient (Ke) is a measure of the amount of drug eliminated from the body per unit of time. Most drugs are eliminated via concentration dependent mechanisms, and Ke is determined from a plot of log of drug concentration versus time. The estimated slope of this line is the Ke for the drug. Usually, Ke has little variability among normal individuals; however, it tends to decrease significantly in patients with renal disease. Drugs that are excreted unchanged by the kidney are subject to the greatest decrease in Ke.

The half-life of a drug can be determined from the Ke value because the two are inversely proportional ($T½ = 0.693/Ke$). As drug clearance decreases, the half-life increases, extending the period of time the drug remains in the body. Clinically, this necessitates decreasing the total daily dose of the drug. The decision to decrease the dose, increase the dosing interval, or both, is often arbitrary; other factors such as cost and patient compliance may also influence this decision. For some medications, drug specific characteristics such as desired plasma concentration (e.g., aminoglycosides) also play a role in determining appropriate patient specific drug regimens.

METABOLISM

There are many drugs that are primarily metabolized by the liver; however, impaired renal function can reduce the activity of the enzymes involved in drug biotransformation. Generally, oxidation, reduction, and hydrolysis reactions are affected more than glucuronidation, sulfation, and glycemic conjugation. More specifically, the hydrolysis of peptides and esters is substantially reduced thereby increasing total drug concentration in the serum.

In renal disease, another important factor in drug metabolism is the production of toxic or active metabolites. Since most metabolites are water soluble and excreted by the kidney, renal failure can result in accumulation of these metabolites. Eventually, these accumulated metabolites may lead to drug toxicity due to potentiation of the action of the parent compound. For example, oxypurinol, a pharmacologically active metabolite of allopurinol, can accumulate in renal failure resulting in adverse effects. Therefore, the dose of allopurinol should be reduced in renal patients. N-acetylprocainamide (NAPA), the major metabolite of procainamide, also accumulates in renal failure. Since NAPA possesses antiarrhythmic activity both similar to, and possibly separate from, procainamide, routine drug level monitoring is recommended for both procainamide and NAPA, with appropriate dosing adjustment performed. Similarly, glyburide, an oral sulfonylurea, is completely metabolized by the liver. Although the metabolites are only mildly active (0.25 to 2.5 percent), accumulation of these compounds over time in patients with renal failure, can lead to pronounced hypoglycemia. Analgesics like codeine, morphine, and hydromorphone are metabolized to compounds that exert a greater analgesic effect than the parent drug. These agents can also accumulate in renal failure and are not readily dialyzed. Their accumulation may lead to excessive sedation and possibly respiratory failure.

Alternatively, a metabolite can have toxicities that are independent of the parent drug. For example, normeperidine has a central nervous system (CNS) stimulatory effect, which may induce grand mal seizures, while the parent drug (meperidine) is an analgesic and CNS sedative. Table 3 lists drugs that are pharmacologically active or have toxic metabolites

Table 3. Effect of metabolites in renal failure

Parent Drug	*Pharmacologic Action*	*Metabolite*	*Comments*
Acebutolol	Antihypertensive	Diacetolol	Metabolite is equipotent
Acetohexamide	Hypoglycemic	Hydroxyhexamide	Metabolite is active and the hypoglycemic effect may be prolonged
Acetaminophen	Analgesic	Conjugated metabolites	Can accumulate and may be toxic in renal failure
Allopurinol	Xanthine oxidase inhibitor	Oxypurinol	Metabolite is responsible for the primary action of the drug
Bupropion	Antidepressant	Hydroxybupropion	Metabolite is half as potent as parent drug
Buspirone	Anxiolytic	Several metabolites	May contribute to longer action of drug
Cefotaxime	Antibiotic	Desacetyl cefotaxime	1/4 to 1/10 as active as parent drug
Chlorpropamide	Hypoglycemic	Hydroxymetabolite	Activity similar to parent in vitro
Clarithromycin	Antibiotic	14-hydroxyclarithromycin	Metabolite is active
Codeine	Analgesic	Norcodeine Morphin-6-glucuronide	May be responsible for prolonged narcotic effect in renal failure patients
Diazepam	Tranquilizer	Desmethyldiazepam	Metabolite is more active than parent compound
Diltiazem	Antihypertensive	Demethylation products	Active metabolite is half as potent as parent compound
Enalapril	Antihypertensive	Enalaprilat	Metabolite is more active than parent compound
Imipramine	Antidepressant	N-monodemethylated metabolite	Half as active as parent drug
Glyburide	Hypoglycemic	Hydroxymetabolite	The hypoglycemic effect of metabolite may be cumulative in renal failure
Meperidine	Analgesic	Normeperidine	Metabolite is less active as an analgesic but can cause CNS stimulation leading to seizures
Methyldopa	Antihypertensive	Methyldopa mono-O-sulfate	Metabolite may accumulate leading to prolonged hypotension
Minoxidil	Antihypertensive	Conjugated glucuronides	Less active than parent compound
Morphine	Analgesic	Morphine-6-glucuronide	May be more active than parent drug: accumulation may lead to prolonged effect
Primidone	Anticonvulsant	Phenylethyl-malonamide Phenobarbital	Metabolite can potentiate parent drug causing toxicity
Procainamide	Antiarrhythmic	N-acetyl-procainamide	Metabolite is a potent-antiarrhythmic
Propoxyphene	Analgesic	Norpropoxyphene	Metabolite has less CNS depressant activity, but more local anesthetic activity
Sodium Nitroprusside	Antihypertensive	Thiocyanate	Metabolite is toxic
Sulfonamides	Antibiotic	N-acetyl sulfonamide	Inactive metabolite, but may be toxic in renal failure patients

that can accumulate in renal failure patients. This table does not include prodrugs, which are designed to be metabolized into active compounds. There is limited information on the effect of hemodialysis on drug metabolites. Furthermore, since the removal of any substance by dialysis is dependent on the length of dialysis, flow rate, and type of dialysis membrane, variability occurs. For this reason, this information was not included. The reader should consult the original drug monograph or the manufacturer for information of this type.

Drugs that are actively secreted by the tubules (ampicillin, cephalexin, and penicillins) can be substantially altered in tubulointerstitial renal disease.

Drug interactions by agents that impair the secretion of these compounds in the proximal tubule may increase drug levels in renal insufficiency. For example, probenecid decreases proximal tubular secretion of methotrexate and penicillins resulting in increased blood levels of these agents. Similarly, quinidine reduces the renal and biliary clearance of digoxin by 30 to 40 percent, thereby increasing digoxin levels.

Tubular reabsorption of a drug may be passive and depends on the pH and pKa of the drug. Nonionized drugs are absorbed more readily than ionized molecules. Weakly acidic drugs (nonionized) will be reabsorbed from acidic urine, whereas basic drugs (ionized) will be excreted in acidic urine. In alkaline urine, the opposite will occur. For example, administration of sodium bicarbonate to increase urinary pH is associated with increased clearance of salicylates. This can result in lower salicylate levels, which could be detrimental in the management of inflammatory conditions, but is desirable in the treatment of salicylate overdose.

CALCULATION OF LOADING DOSE

A loading dose is needed for drugs with a longer half-life in renal failure such as aminoglycosides, digoxin and vancomycin. It takes 3.3 elimination half-lives to reach 90 percent of the steady state concentration of the desired therapeutic level of the drug. In patients with serious infections (common in renal failure), considerable time may be lost in achieving therapeutic concentrations of the antibiotic when a loading dose is not administered. The loading dose should be increased in patients with increased extracellular volume and decreased in dehydration or volume depletion to avoid toxicity. An average value of VD can be obtained from the literature for many drugs. The equation provides the average value of VD for tobramycin (0.34 L/kg) as a starting point to calculate the loading dose.

Loading dose (mg/kg) = Desired concentration (mg/L) x VD (L/kg)

For example, if the desired concentration of tobramycin is 7 mg/L, the loading dose will be:

= 7 mg/L x 0.34 L/kg
= 2.38 mg/kg (given after hemodialysis)

Maintenance dose (mg/kg) = Desired concentration - current concentration (mg/L) x VD (L/kg)

For example, if we assume the current concentration is 1.8 mg/dL, the maintenance dose is:

= (7 mg/L - 1.8 mg/L) x 0.34 L/kg
= 1.7 mg/kg (given after hemodialysis)

It is imperative that all toxic drugs be monitored very closely in these patients.

With the advent of high flux dialysis, the fast removal of a drug over a short period of time can result in a rebound increase in drug concentration, due to redistribution of drug from the tissue compartment to the intravascular space. Therefore, drug levels should be drawn after a new equilibrium is reached so as to avoid overestimation of drug removal in these patients. At least two hours should be allowed for drug equilibration before the levels are drawn. To circumvent these problems it is prudent to administer these drugs postdialysis.

DRUG DOSAGE ADJUSTMENT IN RENAL FAILURE

Determining the appropriate patient specific drug regimen depends on VD, Ke, half-life, and other important pharmacokinetic parameters. However, for clinical purposes, the following tables will summarize suggested dosing adjustments. Table 4 illustrates the dosage adjustments recommended for drugs with significant (50 to 90 percent) renal elimination. These drugs will have extensively prolonged half-lives in renal failure patients, and their total daily dosage must often be decreased by more than 50 percent to prevent toxicity. It is not possible to include every drug that requires adjustment; therefore, only commonly administered drugs are included in this table.

DIALYSIS

The dialysis process affects the removal of solvents across a membrane. Clearance is defined as the amount of drug removed per unit of time. Clearance can differ depending on the type of membrane used during dialysis. The movement of drugs across the dialysis membrane is affected by (1) diffusion, (2) convection, and (3) ultrafiltration.

DIFFUSION

Diffusion is defined as the movement of solute from high to low concentration, down a concentration gradient. This is the primary mechanism of drug removal in dialysis. The movement of molecules is influenced by the type

Table 4. Drug dosing adjustment in renal failure

Analgesics				
Drug	*CrCl > 50 ml/min*	*CrCl 10-50 ml/min*	*CrCl < 10 ml/min*	*Dialyzability*
Butorphanol	2 mg Q3-4 H	1-2 mg Q3-4H	1 mg Q3-4H	H^a P^a
Codeine	30-60 mg Q4-6H	15-45 mg Q4-6H	15-30 mg Q4-6H	H^a P^a
Fentanyl	Individualize dosage	Individualize dosage	Individualize dosage	H^a P^a
Morphine	No change necessary	75% normal dose	50% of normal dose	H^n P^n
Pentazocine	50 mg Q4H	25-50 mg Q4H	25 mg Q4H	H^n P^n
Propoxyphene	65 mg Q6-8H	32-65 mg Q6-8H	Avoid	H^a P^a
Antibiotics				
Drug	*CrCl > 50 ml/min*	*CrCl 10-50 ml/min*	*CrCl < 10 ml/min*	*Dialyzability*
Aminoglycosides	Consult Table	Consult Table	Consult Table	H^y P^y
Amoxicillin	250-500 mg Q8H	250-500 mg Q12H	250-500 mg Q24H	H^y P^y
Amoxicillin/clavulanate	875 mg Q12H	500 mg Q12H	250 mg Q12H	H^y P^y
Ampicillin IV	1-2 gm Q4-6H	1-1.5 gm Q6H	1 gm Q8-12H	H^y P^y
Ampicillin PO	250-500 mg Q6H	250-500 mg Q8-12H	250-500 mg Q12H	H^y P^y
Ampicillin/sulbactam	1.5 gm Q6H	1.5 gm Q8H	1.5 gm Q12H	H^y P^y
Aztreonam	1-2 gm Q8-12H	1 gm Q12-24H	0.5 gm Q12-24H	H^y P^y
Cefazolin	1-2 gm Q8H	0.5-1.5 gm Q12H	0.5 gm Q24H	H^y P^y
Cefepime	1 gm Q12H	1 gm Q16-24H	1gm Q24-48H	H^y P^n
Cefotetan	1-2 gm Q12H	1-2 gm Q24H	0.5-1 gm Q24H	H^y P^y
Cefoxitin	1-2 gm Q6-8H	1-2 gm Q12-24H	0.5-1 gm Q24H	H^y P^y
Ceftazidime	1-2 gm Q8H	1 gm Q12-24H	0.5 gm Q24H	H^y P^y
Ceftizoxime	1-2 gm Q8-12H	1 gm Q12-24H	0.5 gm Q24H	H^y P^y
Cefuroxime	0.75-1.5 gm Q6-8H	1 gm Q12H	0.5-1 gm Q24H	H^y P^y
Cephradine	250-500 mg Q6H	250-500 mg Q12H	250-500 mg Q24H	H^y P^y
Ciprofloxacin IV	400 mg Q12H	Decrease dose by 25%	Decrease dose by 50%	H^y P^y
Ciprofloxacin PO	250-750 mg Q12H	Decrease dose by 25%	Decrease dose by 50%	H^y P^y
Daptomycin	6-8 mg/kg Q24H	6-8 mg/kg Q24-48H	6-8 mg/kg Q48H	H^y P^y
Doripenem	500 mg Q8H	250 mg Q8-12H	No data	H^y P^a
Ertapenem	1000 mg Q24H	1000 mg Q24H	500 mg Q24H	H^y P^a
Imipenem/cilastatin	5-10 mg/kg Q6-8H	5-10 mg/kg Q8-12H	5-10 mg/kg Q12-24H	H^y P^y
Lomefloxacin	400 mg load, then 200 mg Q24H	200 mg load, then 100 mg Q24H	200 mg load, then 100 mg Q48H	H^y P^y
Meropenem	500-1000 mg Q6H	250-500 mg Q12H	250-500 mg Q24H	H^y P^y
Nitrofurantoin	50-100 mg Q6H	Avoid	Avoid	Avoid
Penicillin G	2-3 MU Q4H	2-3 mu Q8H	1 mu Q6H	H^y P^y
Piperacillin	3-4 gm Q4-6H	3-4 gm Q6-8H	3-4 gm Q8H	H^y P^y
Piperacillin/tazobactam	3.375-4.5 gm Q6-8H	2.25 gm Q6H	2.25 gm Q8H	H^y P^y
Streptomycin	1 gm Q24H	0.5 gm Q24H	0.25 gm Q24H	H^y P^y
Sulfamethoxazole	0.5-1 gm Q6H	1 gm Q12-24H	1 gm Q24H	H^y P^y
Sulfamethoxazole /trimethoprim	1 DS Q12H	1 Regular strength Q12H	Not Recommended	H^y P^y
Teicoplanin	6 mg/kg Q24H	6 mg/kg Q48H	6 mg/kg Q72H	H^y P^y

Contd...

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Telavancin	10 mg/kg Q24H	7.5-10 mg Q24-48H	No data	$H^{y} P^{a}$
Ticarcillin/clavulanate	3.1 gm Q6H	3.1 gm Q8H	3.1 gm Q12H	$H^{y} P^{y}$
Vancomycin	15 mg/kg Q12H	15 mg/kg Q24H	15 mg/kg Q72-120H	$H^{y} P^{y}$
Antifungals				
Drug	*CrCl > 50 ml/min*	*CrCl 10-50 ml/min*	*CrCl < 10 ml/min*	*Dialyzability*
Fluconazole	200-400 mg Q24H	100-200 mg Q24H	100 mg Q24H	$H^{y} P^{y}$
Flucytosine	37.5 mg/kg Q12H	37.5 mg/kg Q16H	37.5 mg/kg Q24H	$H^{y} P^{y}$
Antimycobacterials				
Drug	*CrCl > 50 ml/min*	*CrCl 10-50 ml/min*	*CrCl < 10 ml/min*	*Dialyzability*
Ethambutol	15 mg/kg Q24H	7.5-10 mg/kg Q24H	5 mg/kg Q24H	$H^{y} P^{y}$
Para-aminosalicylic acid	50 mg/kg Q8H	Decrease dose by 25-50%	Decrease dose by 50%	$H^{y} P^{y}$
Antivirals				
Drug	*CrCl > 50 ml/min*	*CrCl 10-50 ml/min*	*CrCl < 10 ml/min*	*Dialyzability*
Acyclovir IV	5-10 mg/kg Q8H	5-10 mg/kg Q12-24H	5-10 mg/kg Q24H	$H^{y} P^{y}$
Acyclovir PO	200-800 mg Q4H	200-800 mg Q8H	200-800 mg Q12-24H	$H^{y} P^{y}$
Amantadine	100 mg Q24H	100 mg Q24H	100 mg Q72H	$H^{a} P^{a}$
Didanosine (ddI)	200 mg Q12H	200 mg Q24H	100 mg Q24H	$H^{y} P^{y}$
Foscarnet	Consult package insert	Consult package insert	Consult package insert	
Ganciclovir IV	2.5-5 mg/kg Q12H	1.25-2.5 mg/kg Q24H	1.25 mg/kg Q24H	$H^{y} P^{y}$
Ganciclovir PO	1000 mg Q8H	500-1000 mg Q24H	500 mg 3 x/week	$H^{y} P^{y}$
Lamivudine	150 mg Q12H	Consult package insert	Consult package insert	$H^{y} P^{y}$
Oseltamivir	75 mg Q12H	75 mg Q12-24H	No data	$H^{y} P^{y}$
Stavudine	30-40 mg Q12H	15-20 mg Q12-24H	Insufficient data	$H^{y} P^{a}$
Antihypertensives				
Drug	*CrCl > 50 ml/min*	*CrCl-10-50 ml/min*	*CrCl < 10 ml/min*	*Dialyzability*
Acebutolol	400-600 mg Q24H	200-300 mg Q24H	100-200 mg Q24H	$H^{n} P^{n}$
Atenolol	50-100 mg Q24H	25-50 mg Q24H	25-50 mg Q24H	$H^{n} P^{n}$
Benazepril	10 mg Q24H	5-7.5 mg Q24H	2.5-5 mg Q24H	$H^{n} P^{n}$
Bisoprolol	10 mg Q24H	10 mg Q48H	10 mg Q48-72H	$H^{n} P^{n}$
Captopril	25 mg Q6H	25 mg Q12H	12.5 mg Q24H	$H^{y} P^{n}$
Carteolol	0.5-1 mg Q24H	0.5 mg Q24H	0.25-0.5 mg Q24H	$H^{n} P^{n}$
Digoxin	0.125-0.25 mg Q24H	0.125 mg Q24H	0.125 mg Q48H	$H^{n} P^{n}$
Enalapril	5-10 mg Q12-24H	5-10 mg Q24H	2.5-5 mg Q24H	$H^{y} P^{n}$
Lisinopril	5-10 mg Q24H	2.5-5 mg Q24H	2.5 mg Q24H	$H^{y} P^{n}$
Methyldopa	250-500 mg Q8H	250-500 mg Q8-12H	250-500 mg Q12-24H	$H^{y} P^{n}$
Nadolol	20-80 mg Q24H	Titrate dose	Titrate dose	$H^{y} P^{n}$
Nebivolol	5-40 mg Q24H	2.5-5 mg Q24H, titrate	2.5 mg Q24H, titrate	$H^{a} P^{a}$
Sotalol	80 mg Q12H	80 mg Q24-48H	Individualize dose	$H^{y} P^{n}$
Anti-diabetic				
Drug	*CrCl > 50 ml/min*	*CrCl 10-50 ml/min*	*CrCl < 10 ml/min*	*Dialyzability*
Glimepiride	1.25-20 mg Q24H	1 mg initially, titrate	1 mg initially, titrate	$H^{a} P^{a}$
Glyburide	2.5-5 mg Q24H	Avoid	Avoid	$H^{n} P^{a}$
Saxagliptin	2.5-5 mg Q24H	2.5 mg Q24H	2.5 mg Q24H	$H^{y} P^{a}$

Contd...

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Sitagliptin	100 mg Q24H	25-50 mg Q24H	25 mg Q24H	$H^y P^a$
Miscellaneous				
Drug	***CrCl > 50 ml/min***	***CrCl-10-50 ml/min***	***CrCl < 10 ml/min***	***Dialyzability***
Allopurinol	300 mg Q24H	200 mg Q24H	100 mg Q24H	$H^y P^a$
Cimetidine IV	300 mg Q8H	Decrease by 25%	Decrease by 50%	$H^n P^n$
Cimetidine PO	400 mg Q12H	Decrease by 25%	Decrease by 50%	$H^n P^n$
Colchicine	0.5-1 mg Q24H (up to a 2 mg IV load can be given)	0.5 mg Q24H	0.5 mg Q24H	$H^n P^n$
Duloxetine	60-120 mg Q24H	Lower dose initially, titrate	Avoid	$H^a P^a$
Enoxaparin, prophylactic	30 mg Q12H or 40 mg Q24H	Avoid in CrCl <30 ml/min	Avoid	$H^n P^n$
Enoxaparin, treatment	1 mg/kg Q12H or 1.5 mg/kg Q24H	Avoid in CrCl <30 ml/min	Avoid	$H^n P^n$
Famotidine	20-40 mg Q12H	20 mg Q24H	20 mg Q48H	$H^n P^n$
Fondaparinux treatment	<50 kg, 5 mg q24H 50-100 kg, 7.5 mg Q24H >100 kg, 10 mg Q24H	Caution in CrCl 30-50 ml/min Contraindicated in CrCl <30 ml/min	Contraindicated	$H^y P^a$
Gabapentin	300-600 mg Q8H	300 mg Q12-24H	300 mg Q24-48H	$H^y P^a$
Lithium	TDM	Decrease dose by 25-50%	Decrease dose by 75%	$H^y P^a$
Meperidine	Titrate	Titrate	Not recommended	
Methotrexate	Titrate	Titrate	Titrate	$H^y P^n$
Pregabalin	50-100 mg Q8H	25-150 mg Q12-24H	25-75 mg Q24H	$H^y P^a$
Ranitidine IV	50 mg Q6-8H	Decrease by 25%	Decrease by 50%	$H^y P^y$
Ranitidine PO	300 mg Q24H	Decrease by 25%	Decrease by 50%	$H^y P^y$
Topiramate	100-400 mg Q12-24H	50-200 mg Q24H	100 mg Q24H	$H^a P^a$

H^a – No data available (hemodialysis)
P^a – No data available (peritoneal dialysis)
H^n – None removed (hemodialysis)
P^n – None removed (peritoneal dialysis)
H^y – Removed by hemodialysis
P^y – Removed by peritoneal dialysis
TDM – Therapeutic drug monitoring recommended

of dialysis. Drug properties that allow for a rapid rate of diffusion are low molecular weight, low protein binding, small VD, and low extra-renal clearance. Since most drugs are rendered water soluble for excretion, they are removed along with the water in which they are present.

CONVECTION AND ULTRAFILTRATION

The process of convection is the principle by which drugs are removed by ultrafiltration. Again, high molecular weight drugs are removed slowly as compared to smaller molecular weight drugs. Furthermore, the pore size of the membrane used for dialysis and ultrafiltration becomes an important determining factor for the clearance of drugs. Since most of the membranes used in acute and chronic dialysis are synthetic, adsorption to the membrane can play a significant role, resulting in a decreased amount of drug delivered to the patient. Tobramycin has been shown to adsorb to polyacrylonitrile dialysis membranes. Since the patients are monitored very closely, it is easy to overcome this difficulty in these patients by adjusting the drug dose.

CONTINUOUS RENAL REPLACEMENT THERAPY

In acute renal failure (ARF), continuous renal replacement therapy (CRRT) may be indicated, depending on the etiology of ARF. This consists of continuous arteriovenous hemofiltration (CAVH), continuous arteriovenous hemodialysis (CAVHD), continuous venovenous hemofiltration (CVVH), and continuous venovenous hemodialysis (CVVHD). CRRT is helpful in ARF patients with acid-base abnormalities (acidosis), electrolyte imbalances (hyperkalemia), intoxications (lithium, salicylates, theophylline, ethylene glycol), fluid overload and uremia. Drug clearances attained by CRRT differ from those in chronic dialysis. The removal of drugs during continuous dialysis is much larger compared to chronic dialysis. With CRRT, several unique factors must be considered when determining appropriate drug dosing regimens.

Most of the hemofiltration systems used have a molecular size cutoff of 5000 to 10000 daltons. This is 10 to 40 fold greater than conventional dialysis allowing for greater removal of toxins. However, highly protein bound drugs (phenytoin), are not removed significantly by any form of dialysis, since only free drug can be removed by these methods. Another important consideration in CRRT is the sieving coefficient (Si) of the drug or solute. This is defined as the proportion of drug that will cross the hemofilter membrane. This value is constant for any particular membrane and drug. Compounds with low sieving coefficients have a low degree of removal by this system. The range of sieving coefficients for drugs is zero to one. Drugs with a sieving coefficient of one are fully permeable. The surface area of the hemofilter also affects drug removal. The larger the surface area of the membrane, the larger the solute or drug clearance. Finally, drug removal is increased by increasing the rate of dialysis. Free fraction of drug is correlated with the sieving coefficient of drug hemofiltration. If the dialysate flow through the device is used to increase the efficiency of CRRT, the solutes cross the membrane by diffusion in addition to ultrafiltration. In this case the saturation (Sa) of the combined dialysate and ultrafiltrate with a particular drug is no longer identical after sieving but can be calculated by substituting Sa for Si. The reader is referred to a number of in-depth reviews on CRRT for detailed information (bibliography).

Since different factors can influence the removal of drugs in CVVHD, no absolute drug dosage recommendations can be made. Both CAVHD and CVVHD remove drugs more rapidly therefore, higher replacement drug doses may be required (25 to 50 percent). Therapeutic monitoring of aminoglycosides and vancomycin is indicated in order to maintain adequate therapeutic concentrations. Drug levels are typically drawn one hour before and one to two hours after a dose. For several drugs presented in Table 4, assays are not readily available, therefore clinical judgment must be used so that the patient does not suffer any adverse drug events due to these agents (neurotoxicity, increase in BUN/Cr, increased catabolism, ototoxicity, and nephrotoxicity). Suggestions for drug dosing in CVAH and CVVH are presented in Table 5.

The following drugs are not removed during hemofiltration: azithromycin, ceftriaxone, chloramphenicol, clarithromycin, clindamycin, doxycycline, erythromycin, metronidazole, and amphotericin B.

CONTINUOUS AMBULATORY PERITONEAL DIALYSIS

Continuous Ambulatory Peritoneal Dialysis (CAPD) is another treatment method used to dialyze ESRD patients. This process depends on the peritoneal capillaries performing the job of the dialysis filter. The removal of solutes by CAPD is governed by the same principles as hemodialysis. The drugs used in these patients move across the peritoneal membrane by diffusion and convection. This allows for the unique opportunity to administer drugs intraperitoneally (IP). Not all drugs can cross the peritoneal membrane to the same extent, however most drugs cross easily from the peritoneal cavity into the serum. Movement of drugs from the serum to the peritoneal cavity occurs to a smaller extent. Figure 1 shows the movement of commonly administered drugs in CAPD. CAPD allows for continuous dialysis (over 24 hours) with smooth fluid removal without causing a disequilibrium syndrome. While CAPD offers several

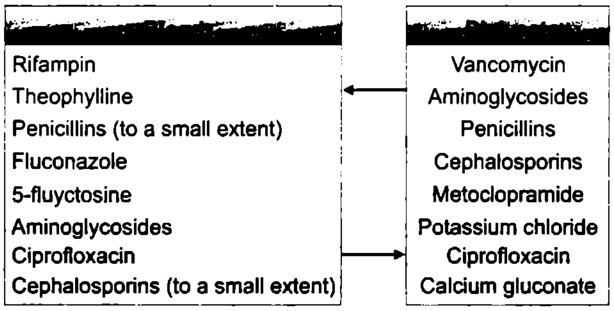

Figure 1: Movement of drugs in continuous ambulatory peritoneal dialysis

advantages such as minimal electrolyte disturbances, it is still not as efficient as other forms of dialysis.

A major drawback to CAPD is the incidence of peritonitis, which is estimated at 1 to 2 percent per patient year. New technologies and improved techniques have decreased the incidence of peritonitis over the last 10 years. In spite of these advances, a large number of catheters are still removed due to infections. Most common pathogens responsible for peritonitis are *Staphylococcus aureus* and *Staphylococcus epidermidis* which account for 75 percent of the cases, followed by Gram negative organisms and fungus. Therefore, it is very important to have guidelines in place for treatment of CAPD peritonitis. Every institution has its own treatment protocol for peritonitis which adheres closely to the most recent guidelines recommended by the Advisory Committee on Peritonitis Management of the International Society for Peritoneal Dialysis. The choice of antibiotics to treat peritonitis depends on the sensitivities of the microorganisms at each institution. Peritoneal infections can be treated by a number of antibiotics, which are listed in Table 6. Most of these antibiotics cross the peritoneal membrane into the serum easily when compared to movement from serum to peritoneal cavity. This has allowed for the IP administration of antibiotics on a weekly or daily basis. It is prudent to start with a loading dose followed by maintenance doses and the therapy can be continued for 7 to 21 days depending upon the response. Once daily dosing of cefazolin and aminoglycosides combinations have been recommended. Similarly, when treating with vancomycin, a single weekly dose has been found to be effective therapy for peritonitis.

Table 5. Dosage changes in CAVH/CVVH

Drug	*Dose in Normal Renal Function*	*Dosage Interval*	*Suggested dose in CAVH/CVVH*
Acyclovir	5-10 mg/kg	Q8H	3.5 mg/kg Q24H
Ampicillin	250 mg – 2 gm	Q6H	250 mg – 2 gm Q6-12H
Aztreonam	2 gm	Q8H	1 gm Q8H
Benzathine penicillin	600 mg – 3.6 gm	Q4Weeks	Decrease by 75%
Cefotaxime	1-2 gm	Q8H	1-2 gm Q12H
Ceftazidime	1-2 gm	Q8-12H	1-2 gm Q24-48H
Cefuroxime	750 mg –1.5 gm	Q8H	750 mg Q12H
Ciprofloxacin	400 mg	Q12H	200 mg Q12H
Fluconazole	200-400 mg	Q24H	200 mg Q24H
Flucytosine	37.5 mg/kg	Q6H	37.5 mg/kg Q12-24H
Ganciclovir	5 mg/kg	Q12H	2.5 mg/kg Q24H
Imipenem/ cilastatin	250 mg-1 gm	Q6-8H	50% of dose Q6-8H
Itraconazole	100-200 mg	Q12H	100 mg Q12-24H
Piperacillin	4 gm	Q6H	4 gm Q8H
Teicoplanin	400 mg	Q24H	400 mg Q48H
Tobramycin	1-1.5 mg/kg	Q8H	50% of dose Q12H TDM
Trimethoprim	100-200 mg	Q12H	100-200 mg Q24H
Vancomycin	15 mg/kg	Q12H	15 mg/kg Q48H TDM

TDM = Therapeutic drug monitoring recommended

Table 6. Drug dosing in CAPD

Drug	*Intermittent Dosing (Dose in a Single Bag)*	*Continuous Dosing (mg/L)*	
		Loading Dose (mg/L)	*Maintenance Dose (mg/L)*
Amikacin	2 mg/kg	25	12.5
Cefazolin	15 mg/kg	500	125
Ceftazidime	1000 mg	250	125
Ceftizoxime	1000 mg	250	125
Ciprofloxacin	500 mg PO Q12H	50	25
Clindamycin	600 mg IV Q8H	300	75-150
Fluconazole PO	-	-	100-200 mg PO QD
Fluconazole IP	-	-	1-3 mg/kg Q48H
Flucytosine PO	-	2000 mg PO	1000 mg PO QD
Gentamicin	0.6 mg/kg	8	4
Imipenem/cilastatin	-	-	25
Piperacillin	4 gm IV Q12H	3 gm IV	250
Sulfamethoxazole/ Trimethoprim	1 DS tab po Q24-48H	5 ml	1.25-2.5 ml
Tobramycin	0.6 mg/kg	8	4
Vancomycin	15-30 mg/kg Q5 days	1000	25

The emergence of vancomycin resistance poses a very difficult problem in the management of peritonitis in CAPD patients. To complicate matters further, it has been shown that the resistance from vancomycin resistant *enterococci* can be transferred to *Staphylococcus aureus*. Vancomycin resistant *staphylococci* are also emerging as a grave hazard to patients. *Staphylococcus* and *streptococcus* species are generally sensitive to first generation cephalosporins but for methicillin-resistant staphylococcus (MRSA and MRSE), vancomycin is currently an alternative agent available. Most patients with peritonitis present with cloudy peritoneal fluid, abdominal pain, fever, increase in white blood cell count (both in the serum and peritoneal fluid), nausea and vomiting, which require immediate therapy.

Fungal infections are generally treated with amphotericin B. Recently, fluconazole, both oral and IP, have been used to treat susceptible *Candida albicans* infection, however, its use has not eradicated fungal peritonitis. Amphotericin B is more effective in the treatment of fungal peritonitis, but it is very irritating and prolonged use can lead to peritoneal fibrosis. In our experience, after treatment of the fungal peritonitis, it was necessary to sacrifice the catheter in our patients due to the increased risk of recurrence.

Gram-negative organisms pose a different challenge and can be treated with aminoglycosides alone or in combination with extended spectrum penicillins (piperacillin) or cephalosporins (ceftazidime). A Gram-negative finding, with or without a Gram-positive organism is clinically suspicious of an intra-abdominal pathology. In cases of mixed cultures, especially if Gram-negative and anaerobic organisms are isolated, a diagnosis of bowel perforation or abscess has to be considered and the patient needs to be aggressively treated with surgical exploration. Metronidazole and clindamycin should be used IP or IV in combination with other drugs for these kinds of serious infections. *Pseudomonas* infections, though treated with the appropriate antibiotics, are very difficult to eradicate because the organism (especially in catheter related infections) protects itself with a biofilm resistant to penetration by antibiotics. *Stenotrophomonas (Xanthomonas)* peritonitis, though not very severe, requires immediate attention and can generally be effectively treated with IP sulfamethoxazole/ trimethoprim.

Failure of therapy should prompt the investigator to look for fastidious organisms, tunnel infections and intracellular organisms in the polymorphonuclear cells (PMN). For reasons not understood, some organisms survive in the PMN, thereby promoting infection when antibiotic treatment has been completed.

Tunnel infections are easy to treat if diagnosed early. It is difficult to salvage the catheter if the infection leads to abscess formation. These infections take a long time to resolve. Treatment of exit site infections includes intranasal mupirocin (1 gram BID for five days) for *staphylococcal* carriers, which has been shown to decrease the incidence of *staphylococcal* infections in these patients. Ciprofloxacin should be added to the regimen to treat tunnel infections. Ceftazidime IP in single doses has been used to treat Gram-negative organisms.

A number of other drugs administered IP are used in the treatment of different conditions in CAPD patients. Table 7 shows the drugs (with doses) commonly used at our institution. Eosinophilic peritonitis can be treated with hydrocortisone. Fibrin formation leading to blockage of the catheter can be initially treated with IP heparin but may necessitate the use of high dose streptokinase to improve the drainage of PD fluid from the cavity. Similarly, some patients cannot tolerate the pain due to instillation of CAPD solution into their PD cavity. In this instance, lidocaine can be used with success.

Electrolyte abnormalities can be treated by administering calcium gluconate for hypocalcemia, and potassium can be added to the dialysate to treat

Table 7. Miscellaneous drug dosing in CAPD

Drug	*Dosing*
Calcium gluconate	1-3 gm /bag
Deferoxamine	125-500 mg/bag
Heparin	500-1000 units/bag
Hydrocortisone	50-100 mg/bag
Insulin (regular insulin)	4-8 units/bag
Lidocaine	30 mg/bag
Metoclopramide	5-10 mg
Potassium chloride	8-10 meq/bag
Streptokinase	2 million units x 1 bag (8-12 hour dwell)

hypokalemia, which is common in these patients. Patients experiencing nausea and vomiting, and gastroparesis, metoclopramide in doses of 5 to 10 mg per bag IP has proved to be very useful. Also insulin can be added to the CAPD bags, though it is a very inefficient method of treating diabetes. Generally the dose ranges from four to eight units of regular insulin per bag.

DRUG-INDUCED NEPHROTOXICITY

A few of the commonly used drugs that cause nephrotoxicity are discussed in this section:

- Aminoglycosides
- ACE inhibitors/ARB drugs
- Amphotericin B
- Cisplatin
- Cyclosporine
- Nonsteroidal Anti-inflammatory Agents (NSAIDs)
- Radiographic Contrast Media
- Drug-induced Crystal Formation and Nephrolithiasis

AMINOGLYCOSIDES

The primary mechanism of aminoglycoside-induced nephrotoxicity involves damage to the proximal renal tubule. Although the exact mechanism has not been fully elucidated, aminoglycosides appear to bind to renal cell membrane phospholipids forming abundant myeloid bodies, destabilizing the cell membrane and ultimately leading to dysregulation of transport mechanisms and cell necrosis. This can result in potassium and magnesium wasting, and loss of concentrating ability. In addition, some evidence suggests that aminoglycosides prevent cell protein synthesis in renal cells in a manner similar to that of bacterial cells. Since aminoglycosides concentrate within the cortex of the kidney, renal dysfunction usually manifests itself several days after the antibiotic is started. However, microscopic changes in the renal brush border and myeloid bodies formation can be detected after the first dose.

Nephrotoxicity is generally related to the duration of therapy and manifests itself after 8 to 10 days. ARF from aminoglycoside therapy is typically nonoliguric and is usually reversible upon discontinuation of the medication. Therapeutic drug monitoring can decrease the likelihood of nephrotoxicity and ototoxicity. Peak serum concentrations generally should fall in the range of 6 to 8 mg/L (or μg/ml) for gentamicin and tobramycin and 25 to 30 mg/L for amikacin. Recommended trough concentrations for gentamicin and tobramycin are less than 2 mg/L and less than 7 mg/L for amikacin. Although the serum levels may be maintained within these ranges, renal toxicity may still occur and renal function should be monitored daily.

In dialysis patients, nephrotoxicity is no longer a concern, but ototoxicity remains a potential complication. As peak gentamicin or tobramycin serum concentrations approach greater than 6 mg/L (or μg/ml), the risk of ototoxicity increases. Ototoxicity may manifest as ringing in the ears, tremor, loss of balance, ataxia, and potentially irreversible loss of hearing. Clinical evaluation and therapeutic drug monitoring are used to potentially decrease the risk of aminoglycoside toxicity. Use of aminoglycosides alone or in combination with other nephrotoxic agents can increase the risk of renal failure, particularly in the elderly, patients with preexisting renal disease, and diabetics. Therefore they should be used cautiously, or alternative agents should be considered. Table 8 gives general guidelines for initiating aminoglycoside and vancomycin dosing for patients with impaired renal function who are on dialysis. Note that the dosing interval, rather than the dose itself, must be adjusted.

ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS

The use of ACE inhibitors has been associated with reversible nonoliguric ARF. This is particularly common in patients with bilateral large-vessel renal artery stenosis or in patients with fixed small-vessel disease (e.g., nephrosclerosis). Patients with low cardiac output and decreased effective circulating volume may have a decrease in renal perfusion. Low renal perfusion leads to compensatory activation of the renin-angiotensin system to maintain adequate renal blood flow. ACE inhibitors inhibit this compensatory mechanism and may cause a profound decrease in perfusion pressure and renal blood flow, resulting in ARF.

AMPHOTERICIN B

The exact mechanism of amphotericin B nephrotoxicity is not well understood, although two proposed mechanisms

Table 8. Aminoglycoside and vancomycin dosing in patients with renal disease

Drug	*Loading Dose*	*CrCl 10-50 ml/min Maintenance Dose*	*CrCl <10 ml/min Maintenance Dose*	*Hemodialysis Maintenance Dose*	*Levels*
Amikacin*	7.5 mg/kg	5-7.5 mg/kg Q12-48H	5-7.5 mg/kg Q48-72H	5 mg/kg after each hemodialysis	1 hour before and 1 hour after dose
Gentamicin*	1.5-2 mg/kg	1-1.5 mg/kg Q12-48H	1-1.5 mg/kg Q48-72H	1-1.5 mg/kg after each hemodialysis	1 hour before and 1 hour after dose
Tobramycin*	1.5-2 mg/kg	1-1.5 mg/kg Q12-48H	1-1.5 mg/kg Q48-72H	1-1.5 mg/kg after each hemodialysis	1 hour before and 1 hour after dose
Vancomycin*	25 mg/kg	19 mg/kg Q24-72H	19 mg/kg Q4-7 days	19 mg/kg Q4-7 days (dependent upon type of dialysis membrane)	1 hour before dose

* Therapeutic drug monitoring is required for all these agents. CrCl = Creatinine clearance.

exist. Amphotericin B may bind to the renal tubule cells, causing an alteration in membrane permeability and resulting in direct cellular toxicity, similar to aminoglycosides. The other proposed mechanism involves the stimulation of the tubuloglomerular feedback system by amphotericin B, resulting in vasoconstriction with a subsequent decrease in GFR. Nephrotoxicity is a common adverse effect of amphotericin B and can occur in up to 90 percent of patients. Nephrotoxicity is reversible with discontinuation of amphotericin B and with adequate hydration; however, permanent damage can occur.

Since amphotericin B remains the only treatment option for certain fungal infections, research on the prevention of nephrotoxicity has been popular. One proposed method is "sodium loading". The infusion of 0.9 percent sodium chloride solution prior to amphotericin B has been shown to prevent nephrotoxicity in some patients, although few well-designed studies exist. This approach, however, is not warranted in patients with congestive heart failure, underlying renal insufficiency, nephrotic syndrome or liver disease, because they are sensitive to sodium loading.

Amphotericin B in a lipid complex has been developed to minimize nephrotoxicity. In this formulation, the amphotericin B is encased in a phospholipid emulsion. It is thought that this protects the renal cells from direct contact with amphotericin B. Numerous reports of decreased nephrotoxicity have been seen with this formulation, but the antifungal efficacy has been questioned because less amphotericin B is available for contact with the fungal cells. Additionally, adverse effects are associated with the phospholipid component, such as cardiopulmonary toxicity and elevated cholesterol and triglycerides. All lipid formulations of amphotericin B are significantly more expensive than the colloidal forms. For these reasons, the lipid preparations should be used judiciously. In cases in which amphotericin B is the only therapeutic option and the risk of nephrotoxicity is high, the use of liposomal amphotericin B may be justified.

NONSTEROIDAL ANTI-INFLAMMATORY AGENTS

NSAIDs commonly induce a form of prerenal ARF by inhibiting prostaglandin formation necessary for vasodilation and maintenance of renal blood flow. All NSAIDs have been implicated in causing renal insufficiency. The cyclooxygenase-2 inhibitors, while less toxic to the gastrointestinal tract, can cause renal impairment in a manner similar to NSAIDs.

Prerenal ARF from NSAIDs occurs when renal prostaglandin production is increased to help maintain blood flow. Underlying conditions associated with impaired renal blood flow and increased renal prostaglandin release include preexisting renal disease, renal artery stenosis, congestive heart failure, elderly patients, diabetics, and volume-depleted patients. NSAIDs may also cause a characteristic lesion manifesting as acute interstitial nephritis and nephrotic syndrome.

The syndrome improves after discontinuation of the offending agent, but immunosuppressive therapy may be necessary. A more detailed description of this lesion is beyond the scope of the current discussion.

CISPLATIN

Cisplatin is concentrated in proximal tubular cells. Nephrotoxicity occurs as a result of cellular degeneration and tubular obstruction from cellular debris, causing acute tubular necrosis. The severity of the lesion is dose and duration dependent and may be irreversible. Predose hydration can limit renal toxicity. Normal saline with or without mannitol or furosemide before and after cisplatin therapy has been effective in providing renal protection.

CYCLOSPORINE

Cyclosporine (CSA) has become the cornerstone drug in the prevention of allograft rejection. It causes a dose-dependent decline in GFR and an associated rise in serum creatinine. CSA frequently leads to renal dysfunction, primarily as a result of renal vasoconstriction. This phenomenon may occur at any dose and at any drug level. Renal function should be monitored frequently and systemic hypertension treated aggressively to reduce the risk of nephrotoxicity. CSA nephrotoxicity is increased by concomitant use of amphotericin B, aminoglycosides, and NSAIDs. A number of agents have been used with varying degrees of success to decrease the risk of the nephrotoxicity caused by CSA, such as:

- Thromboxane A2 synthetase inhibitors
- Pentoxifylline
- Misoprostol

RADIOGRAPHIC CONTRAST MEDIA

The use of contrast media in high-risk patients (with conditions such as diabetes mellitus, preexisting renal failure, multiple myeloma, dehydration, hypertension) is associated with ARF. These agents can cause mild, nonoliguric ARF, with serum creatinine rising within 2 to 3 days and returning to baseline in 10 to 14 days. Oliguric ARF may develop and warrant dialysis. Available contrast agents include hyperosmolar (1500 mOsm/kg) or less hyperosmolar (750 mOsm/kg) forms, although the osmolarity seems to have little influence on the nephrotoxicity caused by these agents. The precise mechanism of nephrotoxicity from these agents is not known. Prevention of nephrotoxicity is more important. Hydration, especially in high-risk patients, seems to be effective in reducing nephrotoxicity. Intravenous saline with sodium bicarbonate is generally effective if this therapy is given 12 hours before contrast study and for 24 hours following contrast study. Acetylcysteine has also been used as a preventive therapy.

DRUG-INDUCED CRYSTAL FORMATION AND NEPHROLITHIASIS

A number of drugs may cause tubular precipitation of drugs, giving rise to crystal formation or Frank nephrolithiasis (Table 9). As with any compound that may precipitate in the tubules, adequate hydration is important in preventing this process.

SUMMARY

Patients with renal insufficiency can present with subtherapeutic or toxic responses to many medications. As discussed, a basic understanding of pharmacokinetic and pharmacodynamic principles will help the practitioner avoid such drug misadventures. The information in this chapter has been limited to the agents most commonly prescribed in general practice. The authors hope that the guidelines provided will be helpful in the medical management of all patients with renal failure.

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Table 9. Drugs causing tubular crystallization or nephrolithiasis

Acyclovir*	Methotrexate*
Azathioprine	Nitrofurantoin
Bactrim® (sulfas)	Triamterene
Ciprofloxacin	Polyethylene glycol* (causes calcium oxalate stones)
Indinavir*	

*May result in diffuse tubular obstruction and acute renal failure.

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SECTION 4

HYPERTENSION

- An Approach to a Patient with Hypertension
- Pregnancy-related Renal Diseases and Hypertension
- Renovascular Disease

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An Approach to a Patient with Hypertension

Anil K Mandal

CLASSIFICATION OF HIGH BLOOD PRESSURE

A classification of high blood pressure (BP) is presented in Table 1 to guide therapy and counsel patients on the risks of untreated or uncontrolled hypertension.

All stages of hypertension are associated with increased risk of cardiovascular diseases (CVD) and renal failure. The higher the BP, the greater is the risk. All stages of hypertension warrant long-term therapy to keep BP under control. Besides BP elevation, other risk factors for CVD include diabetes mellitus, hyperlipidemia, smoking, physical inactivity and obesity. However, the two most important risks are hypertension and diabetes mellitus.

The objectives of this chapter are to convey to the readers of the following message:

1. Outcome of undetected and uncontrolled hypertension
2. Benefits of adequate and sustained control of hypertension
3. Strategies of antihypertensive therapy

The main purpose of writing this chapter is to provide the readers with a comprehensive plan to determine the etiology of hypertension and a therapeutic approach to achieve a sustained control of hypertension. Antihypertensive drugs are numerous and their efficacy in lowering BP is nearly similar. However, their safety and side effects profile differ. Some drugs may be safer than the others especially when hypertension is accompanied by concomitant illness.

OUTCOME OF UNDETECTED AND UNCONTROLLED HYPERTENSION

The vast majority of the patients with hypertension are asymptomatic. In great majority of people, high BP is detected either during physical examination for unrelated problems, employment physical examination, or BP and diabetes detection program offered by various charitable organizations. In most patients hypertension is essential (idiopathic), since no cause can be found. Although most patients with hypertension are asymptomatic at the time of detection, a small percentage of patients are brought to the hospital for stroke, heart failure or renal failure as a result of undetected severe hypertension or inadequately controlled severe hypertension (malignant hypertension).

It is well known that mild to moderate hypertension, if not treated, will likely progress into severe hypertension, and manifest through its ravaging effects on the vascular system, heart, brain and kidneys. The manifestations of target-organ damage include: left ventricular (LV) hypertrophy, LV failure, and arrhythmias; transient ischemic attack or stroke; hematuria, proteinuria, chronic or progressive renal failure; hemorrhages or exudates with or without papilledema in the retina; absence of one or more major pulses in the extremities (except for dorsalis pedis) with or without intermittent claudication; and abdominal aortic aneurysm or dissecting aneurysm of aorta.

Moderate to very severe hypertension (stage 2 to stage 4 hypertension in Table 1) is a common finding in patients admitted for stroke, myocardial infarction, acute congestive heart failure (CHF) with pulmonary edema, renal failure or a combination of two or more of the complications, as already stated. Hypertensive patients are frequently referred to a renal clinic or a nephrologist office for renal insufficiency. Rapid development of hypertension in a previously normotensive subject increases the suspicion of co-existent renal artery stenosis. Similarly, history of headache, angina, or history of previous stroke in a hypertensive patient increases the suspicion of renovascular hypertension. Coronary angiogram with simultaneous renal angiogram in patients with coronary artery disease shows unilateral or bilateral renal artery stenosis in 15 percent of cases. However, significant renal artery stenosis is uncommon.

The three most common ravaging effects of uncontrolled severe and very severe hypertension are stroke, CHF, and renal failure. This is an important message for the patients and the physicians. On the other hand, they can be assured that adequate and sustained control of BP with antihypertensive drug therapy virtually eliminates stroke and heart failure. It is still slightly uncertain, if BP control can provide complete protection from renal failure and myocardial infarction.

A detectable direct effect of uncontrolled hypertension is LV hypertrophy. Increasing numbers of studies are being published showing that presence or absence of LV hypertrophy is an important determinant of the morbidity and mortality in hypertensive patients associated with coronary artery disease or chronic renal failure. Investigators from Cornell Medical center in New York reported a relationship between LV mass index (normal = ≤125 gm/m^2) and morbid events, including cardiac death, myocardial infarction, stroke, or angina requiring revascularization in a 10-year follow-up study of 280 hypertensive men and woman. Hypertensive patients with LV mass index >125 gm/m^2 were at strikingly greater risk for cardiovascular and all-cause mortality than those with lower LV mass index. The risk of adverse events was also highest in those with concentric LV hypertrophy (characterized by increase in both the ratio of LV wall thickness to chamber radius and LV mass), and lowest in those with normal LV geometry. Most commonly, LV hypertrophy results in diastolic dysfunction which gives rise to elevated LV filling pressure and pulmonary venous congestion and manifesting in dyspnea on exertion, paroxysmal nocturnal dyspnea, orthopnea or pulmonary edema.

Table 1. Classification of blood pressure for adults

Category	*Systolic (mmHg)*	*Diastolic (mmHg)*
Normal	<130	<85
High Normal	130-139	85-89
Hypertension **		
Stage 1 (mild)	140-159	90-99
Stage 2 (moderate)	160-179	100-109
Stage 3 (severe)	180-209	110-119
Stage 4 (very severe)	≥210	≥120

Not taking antihypertensive drugs and not acutely ill. Isolated systolic hypertension (ISH) is defined as SBP > 140 mmHg and DBP <90 mmHg and staged appropriately (e.g., 170-85 mmHg is defined as Stage 2 ISH).

** Based on the average of two or more readings taken at each of two or more visits following an initial screening.

Less commonly, LV hypertrophy results in systolic dysfunction which gives rise to LV dilatation, reduced ejection fraction, increased-end diastolic volume and low-output CHF. Two patients are illustrated here to exemplify the devastating effects of uncontrolled severe hypertension on heart and kidneys.

1. A 43-year-old white male was admitted into hemodialysis unit for regular maintenance hemodialysis at a local hospital in Dayton, Ohio after being transferred from Gainesville, Florida. He was very severely hypertensive; BP was in the range of 220 to 240 mmHg systolic and 130 to 140 mmHg diastolic. Chest X-ray showed huge cardiomegaly. Echocardiogram showed increased LV mass and small amount of pericardial effusion. He was treated with numerous antihypertensive drugs, consisting of ACE inhibitors, calcium channel blockers, labetalol and central inhibitors and three times weekly hemodialysis. Finally his BP was brought under control and remained adequately controlled. Concomitantly, serial chest X-ray showed a normal cardiac silhouette in parallel with control of BP. Patient received a cadaveric renal transplant, but soon he rejected his grafted kidney. Patient again developed uncontrolled severe hypertension, marked cardiomegaly and CHF. He was treated with hemodialysis. BP remained

uncontrolled. Continuous ambulatory peritoneal dialysis was initiated which results in control of BP, reversal of cardiomegaly and remission of CHF.

2. A 25-year-old African-American male, had numerous admissions to a local hospital in Oklahoma City, Oklahoma for investigation and management of hypertension. He presented to the general medicine clinic for the first time in November 1972 with the complaint of a persistent headache for four days and was found to have BP 240/140 mmHg and grade II retinopathy (arterial narrowing and arteriovenous compression). Serum urea nitrogen and serum creatinine concentrations were 27 and 2.3 mg/per dL, respectively. A complete workup failed to demonstrate an underlying cause for hypertension. A wedge biopsy of the kidney was performed and renal tissue was studied using light microscopy (LM), transmission electron microscopy (TEM), and immunofluorescence microscopy (IFM). Although LM study showed slight thickening of the vessels, TEM of an arteriole showed remarkable changes consisting of atrophy, necrosis, and hyperplasia of SMC, small amounts of collagen fibers, and electron-dense deposits. These findings suggested severe vascular changes in the kidneys. These vascular changes reflected likelihood of developing severe clinical manifestations later on.

The patient was placed on antihypertensive therapy, his headache promptly disappeared, and the serum urea nitrogen and serum creatinine fell to near normal values. On routine visit to the renal clinic, he was found to have marked elevations of BP in excess of 240/140 mmHg on numerous occasions, many of which required short-term hospital admissions for control of BP. However, the serum urea nitrogen and serum creatinine concentrations were always below those observed at his first admission. After 36 months, he had a sudden onset of exertional dyspnea, followed by paroxysmal nocturnal dyspnea and oliguria, and was admitted to the hospital. His BP was in the range of 250 to 260 mmHg (systolic) and 140 to 150 mmHg (diastolic), and the fundi showed grade III retinopathy (hemorrhage, exudate). He had rapid deterioration of renal function with an increase in serum urea nitrogen and serum creatinine concentrations to 110 and 11.5 mg/per 100 ml, respectively. After treatment with large doses of antihypertensive drugs, including intravenous administration, along with digitalis and diuretics, his BP was controlled and the serum urea nitrogen and serum creatinine concentrations decreased to 80 and 8.5 mg/100 ml, respectively. Eight weeks following this episode, his renal function again deteriorated, BP increased, and he was placed on the maintenance hemodialysis program. Despite treatment with hemodialysis and massive doses of antihypertensive drugs, his BP continued to rise. He underwent bilateral nephrectomy 43 months after the initial biopsy and the renal tissue was studied by LM, TEM, and IFM.

The LM study revealed more severe change compared to that in the initial biopsy. Some arterioles demonstrated marked intimal thickening and SMC hyperplasia; still others showed loss of endothelial cells and occlusion of the lumina. Intense PAS-positive material suggestive of necrosis in the intima and occlusion of the lumina by thrombi was observed in some arterioles. About 60 percent of the glomeruli revealed marked, irregular thickening of the peripheral capillary loops. Twenty percent of the glomeruli were hyalinized and revealed fibrotic crescents; an equal number showed necrosis of capillaries and plasma material into Bowman's space. Few glomeruli appeared normal. The tubules were variable; some being normal, some were atrophic, while others dilated and filled with casts. Ten to twenty percent of the tubules showed necrotic changes and a few tubules were filled with red cells.

Electron microscopy study of arterioles demonstrated predominant hyperplasia of smooth muscle cells (SMC) in one arteriole to mainly necrosis of SMC in another arteriole. In general, the arteriolar changes were more severe and widespread than those observed in the biopsy specimen. TEM of glomeruli revealed irregular but pronounced thickening and tortuosity of glomeruli in most capillaries, necrosis of some capillaries with discrete electron-dense deposits, atrophy of endothelial cells, crescent formation, or exudation in Bowman's space.

The lesson learned from these examples is that heart failure or renal failure might have been prevented provided BP was kept under adequate control. Both patients were noncompliant and not taking prescribed medications regularly. Both SBP and DBP remained all time high and as a result, severe heart and renal damage was sustained.

Benefits of Adequate Control of Hypertension

Since essential hypertension is mostly asymptomatic, it is sometimes difficult to convince a hypertensive patient who has no symptoms or show no abnormal laboratory findings about the benefits of adequate and sustained control of hypertension. The asymptomatic state of hypertension fraught with the side effects of the antihypertensive drugs is the principal determinant of the noncompliance of the patients in taking medication. However, patients and their families should be appraised of the fact that before hypertension detection and treatment programs became available, the common causes of death in untreated or uncontrolled hypertensive patients were heart failure, stroke, and uremia. Numerous studies have confirmed the benefits in treated hypertensive patients compared to those who remained untreated. Sir George Pickering of United Kingdom found the above as the cause of death in his untreated hypertensive patients. Reduction of both SBP and DBP to normal or near normal levels and maintenance of BP at that levels have shown to: (a) reduce the incidence of strokes and death due to strokes; (b) dramatically reduce the incidence of CHF, and (c) reduce the incidence of death from coronary heart disease (d) delay or prevent the development of renal failure.

The following studies exemplify the benefits of adequate and sustained control of hypertension:

1. The results of the European working party on high BP in the elderly is an example of the overall benefit of antihypertensive drug therapy. This study recruited 840 patients with a mean age of 72 years. The criteria for inclusion in this study were a systolic BP in the sitting position between 150 and 239 mmHg and a diastolic BP between 90 and 119 mmHg. The patients were randomly assigned to receive active treatment (HCTZ and triamterene) or placebo treatment. In case of an insufficient decrease in BP, methyldopa was added to the regimen. A significant reduction in the mortality rate (-36 percent) was observed in the group receiving active treatment. These results are identical to those of Veterans Administration Cooperative Study Group and the trial of the Australian National Blood Pressure Study Management Committee. The rate of mortality of cardiac origin, including sudden death, was significantly reduced (-47 percent), whereas the number of nonfatal myocardial infarctions was slightly higher in the treated group. Treatment also reduced the incidence of episodes of severe heart failure (-63 percent), but no significant difference was observed for moderately severe episodes of cardiac decompensation. Finally, mortality of cerebrovascular origin was reduced by treatment, but the difference with placebo was not statistically significant. The results of these various studies demonstrate that the treatment of hypertension in elderly patients globally reduces cardiovascular and cerebrovascular morbidity and mortality.
2. We did a retrospective analysis of the relationships between BP control, hematocrit levels and renal function in 97 treated hypertensive patients at entry and at four anniversary dates thereafter. The patients were divided into two groups: Group I and Group II on the basis of dose of hydrochlorothiazide (HCTZ) used. Group I received an average dose of 100 mg HCTZ daily, whereas Group II received an average dose of 50 mg HCTZ daily. In Group I, the decrements in both systolic and diastolic BP overtime was highly significant ($P<.001$); however, no change in renal function was noted. In Group II, systolic BP decreased significantly ($P<.01$) from entry to year 1, then leveled off. In year 4, systolic BP was not different from that of entry. On the other hand, the difference between entry and year 4 diastolic BP was highly significant ($P<.0001$). In Group II, significant decreases were noted in serum urea nitrogen and serum creatinine levels between entry and year 4. Hematocrit showed adverse response; in Group I, hematocrit significantly increased from entry to year 4, whereas, in Group II, hematocrit significantly decreased. A separate analysis between African Americans and Whites showed that African-American patients did better with high does of HCTZ in both BP control and maintenance of renal function, whereas white subjects tend to do better with low dose HCTZ. This study concludes that high dose HCTZ is beneficial for African-American hypertensives; however, low dose HCTZ appears to be universally beneficial.

SYSTEMATIC APPROACH TO A PATIENT WITH HYPERTENSION

Every patient with hypertension should be thoroughly evaluated to determine if the patient under consideration has: (i) essential hypertension; (ii) hypertension due to renovascular disease (renovascular hypertension); (iii) hypertension due to an endocrine cause (primary hyperaldosteronism; (iv) hypertension associated with diabetes mellitus; (v) hypertension associated with hypokalemia without the use of a diuretic; and (vi) hypertension associated with renal failure.

A good history taking and a thorough physical examination are essential. Examination should seek for the possibility of secondary hypertension. Physical findings suggestive of secondary hypertension include: abdominal or flank masses (polycystic kidneys); abdominal bruits in periumbilical area (renovascular disease); delays or absent femoral pulses and decreased BP in lower extremities compared with the upper extremities (aortic coarctation); truncal obesity with purple striae (Cushing syndrome); and tachycardia, tremor, orthostatic hypotension, sweating, and pallor (pheochromocytoma).

Like history and physical examination, certain baseline laboratory studies should be done before initiation of pharmacologic interventions. The results of these baseline studies will aid in determining the type of drug and dosing intervals and in detecting adverse effects at the early stage. These assessments include: (i) urinalysis; (ii) urinary electrolytes (Na^+, K^+, Cl^-) and creatinine (random urinary sample is fine; 24-hour urine collection is not necessary); (iii) chest X-ray; and (iv) echocardiogram if cardiomegaly is noted in chest X-ray.

Antihypertensive drug therapy should be initiated upon first visit if a patient has stage II or stage III hypertension, and one or more of the following concomitant features: (i) persistent headache; (ii) waning consciousness; (iii) signs of heart failure; (iv) angina; (v) diabetes mellitus; (vi) cardiac arrhythmias; and (vii) renal failure.

Besides prescription of antihypertensive drug therapy, patients should be counseled to develop a habit of moderation and to avoid excesses (lifestyle change). Lifestyle moderation by avoiding excesses in food, salt intake, and alcoholic beverages, as well as complete refrain from smoking will be complementary to drug therapy. These nonpharmacologic interventions are effective in lowering BP of subjects who follow them rigidly. Restriction of salt intake can be most rewarding in patients who show evidence of CHF. However, restriction of salt intake should be monitored by urinary sodium excretion as inadvertently excessive restriction of salt intake could lead to volume depletion and renal failure, especially in the elderly subjects.

Lifestyle modifications are particularly helpful in the hypertensive patients who have additional risk factors for premature CVD, especially diabetes mellitus or dyslipidemia. There is increasing publicity about the importance of high potassium and calcium-containing foods in the protection against high BP. An increased calcium intake may lower BP in some patients with hypertension, but the overall effect is minimal. The prescription of high potassium diet is a dangerous proposition because of the high risk of developing hyperkalemia even with normal renal function. The risk is greater in the presence of mild renal failure and life-threatening in the face of severe renal failure.

Strategies of Antihypertensive Therapy

Objectives of Antihypertensive Therapy

a. To achieve effective control of BP
b. To reduce LV mass
c. To prevent death from target organ damage such as heart failure, stroke or renal failure
d. To preserve the quality of life

Profile in Drug Selection

Choice of Antihypertensive Drug Therapy

Choice of antihypertensive drug therapy will depend on the following factors which include age, race, weight, level of pretreatment BP, status of left ventricle, renal function, concomitant conditions, such as coronary artery disease, diabetes mellitus, hyperlipidemia, quality of life status, adverse effects and cost.

Choice of Antihypertensive Therapy

Drugs that may be used singly or in combination are:

1. Thiazide diuretic
2. Beta adrenoreceptor blocker
3. Calcium channel blocker
4. Angiotension converting enzyme (ACE) inhibitor
5. Central inhibitor:
    a. Clonidine
    b. Methyldopa
    c. Reserpine
6. Alpha adrenoreceptor blocker
    a. Prazosin
    b. Doxazosin

7. Combined alpha and beta adrenoreceptor blocker
   a. Labetalol
8. Peripheral vasodilator
   a. Hydralazine
   b. Minoxidil

Principles of Antihypertensive Therapy

Thiazide Diuretics

Step-care approach with a thiazide diuretic as a first step therapy has fallen in disrepute, mainly caused by the use of very high dose of thiazide diuretic (100 to 150 mg per day) in the past, which resulted in life-threatening or fatal cardiac arrhythmias in some patients. However, thiazide diuretic, such as HCTZ or chlorthalidone in low dose of 12.5 mg or 25 mg per day effectively controls BP in most mild hypertensive subjects, irrespective of the age and race. It is most effective in lowering BP in African Americans, as already stated. Sometimes, 25 mg per oral twice daily is required to control BP adequately. Thiazide diuretics potentiate the effect of most antihypertensive drugs and helps control of BP in resistant hypertension, even in patients with renal insufficiency. The exact mechanism of the antihypertensive effect of thiazide is still unclear. However, it does not appear to reside entirely on the natriuretic effect. Hypokalemia of mild severity (3 to 3.5 mEq/L) is common, however, it should not be deterrent to the use of thiazide diuretic. Serum potassium (K^+) initially should be monitored every two to four weeks. Decrease in serum K^+ should be treated with K^+ supplementation. Rapid decrease of serum K^+ by 1 mEq/L or more every one to two weeks suggests an underlying avid potassium-secretory state, such as primary or secondary hyperaldosteronism. Potassium 20 mEq once or twice daily should be given from the time of initiation of thiazide diuretic in patients who are receiving digitalis preparation or in those with a history of myocardial infarction. Concomitant use of an ACE inhibitor has been advocated to avert the hypokalemic effect of thiazide diuretic. ACE inhibitors suppress angiotensin (A) II production, thereby inhibit aldosterone production, hypoaldosteronism results in K^+ retention in the renal tubule cells. This is an improper way to prevent hypokalemia as ACE inhibitor used in conjunction with a diuretic has a high risk of causing acute renal failure (ARF). If an ACE inhibitor has to be added to the regimen for control of BP or CHF, then K^+ supplementation should be avoided as this combination may cause severe hyperkalemia. Thiazide diuretic may be combined with a potassium sparing agent such as triamterene or amiloride, to prevent hypokalemia. There are several combined preparations available in the market such as maxide® or dyazide®. However, in patients with impaired renal function, this combination has a high risk of causing hyperkalemia.

Thiazide diuretic induces a variety of metabolic abnormalities, such as impaired glucose tolerance, hyperlipoproteinemia and hyperuricemia. Therefore diuretic use should be avoided or cautiously used in patients with diabetes, gout or hyperlipidemia (for details of side effects of diuretics, see Chapter on Generalized Edema). Thiazide diuretics may cause symptomatic hyponatremia especially in elderly women.

Beta Blockers

Beta adrenoreceptor blockers include propanolol, (Inderal®) or cardioselective atenolol (Tenormin®) or metoprolol (Lopressor®). While propanolol is given as 10 to 40 mg three to four times daily, atenolol 50 to 100 mg once-a-day dosage is quite effective. Metoprolol is given 50 to 100 mg twice daily.

Beta blockers used as monotherapy lowers BP with normal or high plasma renin activity (PRA) irrespective of age. However, it is more effective in younger hypertensives and white Americans than in elderly hypertensives and African-American hypertensives. Beta blocker is a good drug to use in hypertensives with cardiac arrhythmias such as premature ventricular beats or atrial tachycardia, and is a good adjuvant with vasodilators or calcium channel blockers which induce tachycardia as a result of reflex sympathetic activity. Unlike other antihypertensive drugs, beta blockers offer additional benefits over and above BP reduction. Beta blockers reduce endogenous catecholamine levels, and plasma renin, thereby reduce cardiac output and heart rate, reverse (reduce) LV mass, decrease incidence of reinfarction and increase in ventricular fibrillation threshold. Further, beta blockers reduce the number of symptomatic ischemic episodes, and minimize increase in heart rate during exercise or excitement.

A beta blocker in combination with a thiazide diuretic is additive in lowering BP, but hyperlipidemia and insulin resistance may worsen with this combination therapy. Beta blockers should be avoided in patients with history of asthma, chronic bronchitis or chronic obstructive lung disease. Even cardioselective ones should be used with some caution in diabetes for the possible risk of masking hypoglycemia due to blunted sympathetic response. Severe hyperkalemia may develop in patients with acute or chronic renal failure due to inhibition of epinephrine, which causes intracellular translocation of K^+ and tends to avert dangerous hyperkalemia in potassium overload states. Therefore beta blocker should be avoided or used with caution in renal failure patients.

Calcium Channel Blockers

This group of drugs lowers BP in hypertensive subjects of all ages. They are especially effective in elderly hypertensives, and safe in patients with asthma, emphysema, gout, diabetes or peripheral vascular disease. This group of drugs appears to be the prime target of antihypertensive therapy because of their effect on vascular smooth muscle cells (VSMCs) and the effect may be mediated by inhibition of novel vasoconstrictor peptide similar to endothelin-1. Endothelin induces vasoconstriction in a variety of vascular beds, possibly directly or indirectly by influx and accumulation of Ca^{2+} into VSMCs. Thus, it is possible but not proven that, by inhibiting the effect of endothelin-1, calcium channel blockers induce relaxation of VSMCs. Among numerous calcium channel blockers available in the market, second-generation dihydropyridine compounds including amlodipine (Norvasc®), felodipine (Plendil®), or isradipine (Dynacirc®) are more commonly used than first generation dihydropyridine compounds or nondihydropyridine compounds. All three second generation dihydropyridine are almost similar in their effect to lower BP. However, side effects consisting of uncomfortable palpitation and tachycardia are more pronounced and are observed in higher percentage of patients treated with felodipine than with amlodipine or isradipine. Second generation dihydropyridine compounds have minimal negative ionotropic effect unlike nondihydropyridine compounds and generally are safe to use in patients with heart failure or heart block.

Nondihydropyridine compounds, including diltiazem or verapamil, are equally effective like dihydropyridine compounds in lowering BP but due to the negative ionotropic effect they are not safe in patients with heart failure or heart block. In addition, verapamil is well known to cause severe constipation and, therefore, not safe in elderly or debilitated patients.

Nondihydropyridine calcium channel blockers should be avoided in patients receiving a digitalis preparation, as this combination may cause severe bradycardia. On the other hand, both these drugs are effective in controlling atrial arrhythmias. In terms of hypotensive potency, nifedipine is more potent than any other calcium channel blocker. Given sublingually 10 mg nifedipine produces profound vasodilatation and dramatically reduces BP. It has an onset of action within three minutes with a peak effect within one hour. Thus, this drug was very popular among the junior doctors in treating very high BP or hypertensive emergencies. Nifedipine given orally does not work as fast as it does sublingually. However, this severe vasodilatation is accompanied by marked reflex sympathetic activity which gives rise to tachycardia, flushing and palpitation and produce much discomfort to the patients. In addition, nifedipine causes sodium retention giving rise to edema or aggravation of heart failure. Therefore nifedipine should be avoided to treat hypertension, if possible. The author doesn't use that drug. Second generation dihydropyridine such as amlodipine or felodipine causes edema. Edema is uncommon with isradipine.

ACE Inhibitors

ACE inhibitors reduce angiotensin II formation, thereby decrease peripheral vascular resistance and cause fall in BP. Besides vasodilator action, other mechanism(s) possibly add to the hypotensive effect. These mechanisms include increase in blood bradykinin level due to the inhibition of enzyme kininase. Bradykinin stimulates production of PGE2, which potentiates the vasodilatory effect and causes natriuresis. Increased urinary Na^+ excretion is observed in patients treated with ACE inhibitors. There are numerous ACE inhibitors on the market and it is difficult to choose a particular one. Some are short acting, such as captopril, and can be given three to four times daily, whereas others are long acting and can be given once or twice daily. The kidneys clear these drugs. Therefore, dosage adjustment is necessary in patients with renal failure. There is great publicity about the benefits of ACE inhibitors in diabetic nephropathy and CHF. The author finds no rationale in that publicity and observes more side effects than benefits. The claim of investigators that ACE inhibitors delay dialysis in diabetic nephropathy cannot be substantiated in author's intensive observational studies. Similarly, the claim of benefit of these drugs in CHF is far from reality.

Two most common adverse effects that tend to deter the use of ACE inhibitors are renal insufficiency and hyperkalemia. Several studies have reported development of renal insufficiency of variable severity, including ARF, following the use of ACE inhibitors in hypertensive patients with bilateral renal artery stenosis or renal artery stenosis in a solitary kidney. A rather popular mechanism in explaining the development of renal failure is efferent arteriolar dilatation resulting in fall of glomerular capillary pressure and rapid decrease in GFR. However, ARF has developed in patients with unilateral renal artery stenosis with anatomically normal contralateral kidney in our experience, and this has been the experience of other investigators also. These observations tend to refute the idea of efferent arteriolar dilatation as the sole mechanism of ARF.

In a recent retrospective analysis of hypertensive patients treated with ACE inhibitors, we have found that ACE inhibitors given alone are unlikely to produce ARF. However, the risk of ARF is significant when ACE inhibitors are given concomitantly with a diuretic. Further, ARF reverses upon discontinuation of ACE inhibitor and diuretic and repletion of volume with normal or half-normal saline, suggesting sodium-volume depletion or decreased renal perfusion as an important determinant of ARF.

Central Inhibitors

The most commonly used central inhibitor is clonidine. Another central inhibitor is reserpine, but it is used sparingly nowadays. These drugs are central alpha receptors agonists. Specifically, when these alpha receptors, which are situated in the area of nucleus tractus solitarius of the medulla oblongata are activated, there is a decrease in sympathetic outflow to the cardiovascular system. Therefore this central agonist property produces inhibitory effects on peripheral sympathetic activity. In fact, it has been shown that pretreatment with the alpha receptor blocking agents phentolamine will antagonize clonidine's BP lowering effect.

Clonidine given orally in a dose of 0.05 to 0.1 mg twice daily effectively lowers BP. Major side effects include drowsiness, dry mouth and sexual dysfunction. With 0.4 to 0.6 mg daily intake, side effects can be severe and often result in discontinuation or withdrawal of the drug. Diuretics potentiate the antihypertensive effect of clonidine and this combination can adequately control BP in mild to moderate hypertension. Clonidine is most effective in lowering BP in African-Americans and is considered the best antihypertensive drug in that race.

Methyldopa has central and peripheral effects. It is a central alpha receptor agonist. Peripherally, alpha-methyl norepinephrine like norepinephrine is taken up by adrenergic nerve endings. This alpha-methyl norepinephrine competes with norepinephrine at the postsynaptic alpha-adrenergic receptor. It is a slow-acting drug, taking six hours to produce effect after an oral dose, but effect may persist up to 48 hours. Sexual dysfunction and drowsiness are very common side effects and frequently result in discontinuation of the drug. However, methyldopa is a safe drug to treat hypertension in pregnancy. The usual dose is 250 mg per oral three or four times daily. The dose can be increased to 500 mg three or four times daily, if the patients can tolerate.

Reserpine depletes norepinephrine and serotonin stores in the brain and peripheral nerve endings. Reserpine works in a fashion different from that postulated for clonidine or methyldopa and appears to have an inhibitory effect on adrenergic mechanisms rather than the agonist action. This drug in once daily dosage effectively lowers BP and is inexpensive. Usual dose is 0.05 to 0.1 mg daily. Maximum dose is 0.5 mg per oral daily. However, this drug also produces side effects similar to those by clonidine and methyldopa.

Peripheral Vasodilators

Peripheral vasodilators include hydralazine, prazosin, labetalol, and minoxidil. These are very potent hypotensive drugs. Labetalol has a rapid onset of action and produces a smooth reduction in BP. Prazosin and labetalol are well known in producing symptomatic postural hypotension. Dizziness is very common and syncope is not uncommon with these two drugs. Therefore, these drugs should be started in a very small dose, like prazosin 0.5 mg twice daily and labetalol 50 mg twice daily, and dose should be gradually titrated upwards to achieve control of BP.

Hypertensive patients on maintenance hemodialysis are very sensitive to these drugs, because of volume depletion in these patients. The result is dizziness or syncope. Hydralazine 25 to 50 mg every six to eight hours is an effective antihypertensive drug. This is a drug of choice in hypertension of pregnancy. For the details of the treatment of hypertension in pregnancy, the readers should review the chapter on Pregnancy-related Renal Disease and Hypertension. High dose (400 mg/day) given for a prolonged period of time may give rise to lupus syndrome. Hydralazine is a direct arteriolar vasodilator that causes a secondary baroreceptormediated sympathetic discharge resulting in tachycardia and increased cardiac output. Reflex tachycardia produced by vasodilation makes these drugs less than ideal to use in hypertensive patients with a history of, or overt evidence of coronary artery disease. Tachycardia will increase myocardial oxygen consumption, resulting in exacerbation of angina. All vasodilators, especially minoxidil, cause sodium and fluid retention and may give rise to edema and CHF. Minoxidil additionally may produce pericardial effusion. Concomitant use of a diuretic is recommended along with a vasodilator.

Individual Antihypertensive Therapy

Antihypertensive drug(s) should be chosen based on profile on drug selection. Therapy should be initiated with one drug, and depending on the response, dose adjustment of the same drug, substitution by another drug, or addition of a second drug should be made. Choice of drug(s) will also depend on concomitant conditions.

Management of Hypertension in the Elderly

Several large placebo-controlled trials of antihypertensive treatment in the elderly have been published. The results of these studies are encouraging and provide necessary database to recommend antihypertensive drug therapy in the elderly. However, on the basis of these studies extent of enthusiasm for aggressive treatment of hypertension in the elderly should be dampened. The reason for dampening the enthusiasm is the side effects of the drugs, which may be quite severe in the elderly. A major side effect of antihypertensive therapy in the elderly is postural hypotension, which often causes them to fall and to sustain hip fracture. This type of dangerous outcome must be carefully weighed against the dubious benefit of antihypertensive therapy in the elderly, especially in those with mild or questionable hypertension.

According to the experience of the author of this chapter, useful and reasonably safe antihypertensive drug therapy for the elderly include the following drugs singly or in combination:

1. HCTZ 12.5 to 25 mg po daily. Serum K^+ supplementation be given as necessary. It is important to know that HCTZ can be increased to 50 mg po daily for effective control of BP in resistant hypertension.
2. Atenolol 25 to 50 mg/daily.
3. Combination of HCTZ (12.5 mg/daily) and atenolol (25 mg/daily).
4. Clonidine 0.05 to 0.1 mg once or twice daily.
5. Amlodipine 5 mg once or twice daily.
6. Amlodipine 5 mg + HCTZ 12.5 mg/daily. Serum K^+ should be monitored and K^+/supplementation given as necessary.

The guidelines in Table 2 may be followed in treating hypertension in the elderly.

FOCUS

Importance and Appropriate Use of Antihypertensive Therapy in Preservation of Renal Function

Unrecognized, untreated and/or uncontrolled hypertension is the second most common cause of end stage renal disease (ESRD). Diabetic nephropathy is the most common cause of ESRD. This is shown in Figure 1. *It is important to know that many of the diabetes-ESRD* can be severely hypertensive which leads to progression of diabetic nephropathy into ESRD in an accelerated rate.

It is equally important to understand that keeping BP at or near normal level (130 to 140 / 80 to 85 mmHg) with drug therapy which has or no adverse effect on the kidneys is conducive to preservation of reasonable amount of renal function (for instance serum creatinine ≤3 mg/dL or estimated glomerular filtration rate (eGFR)

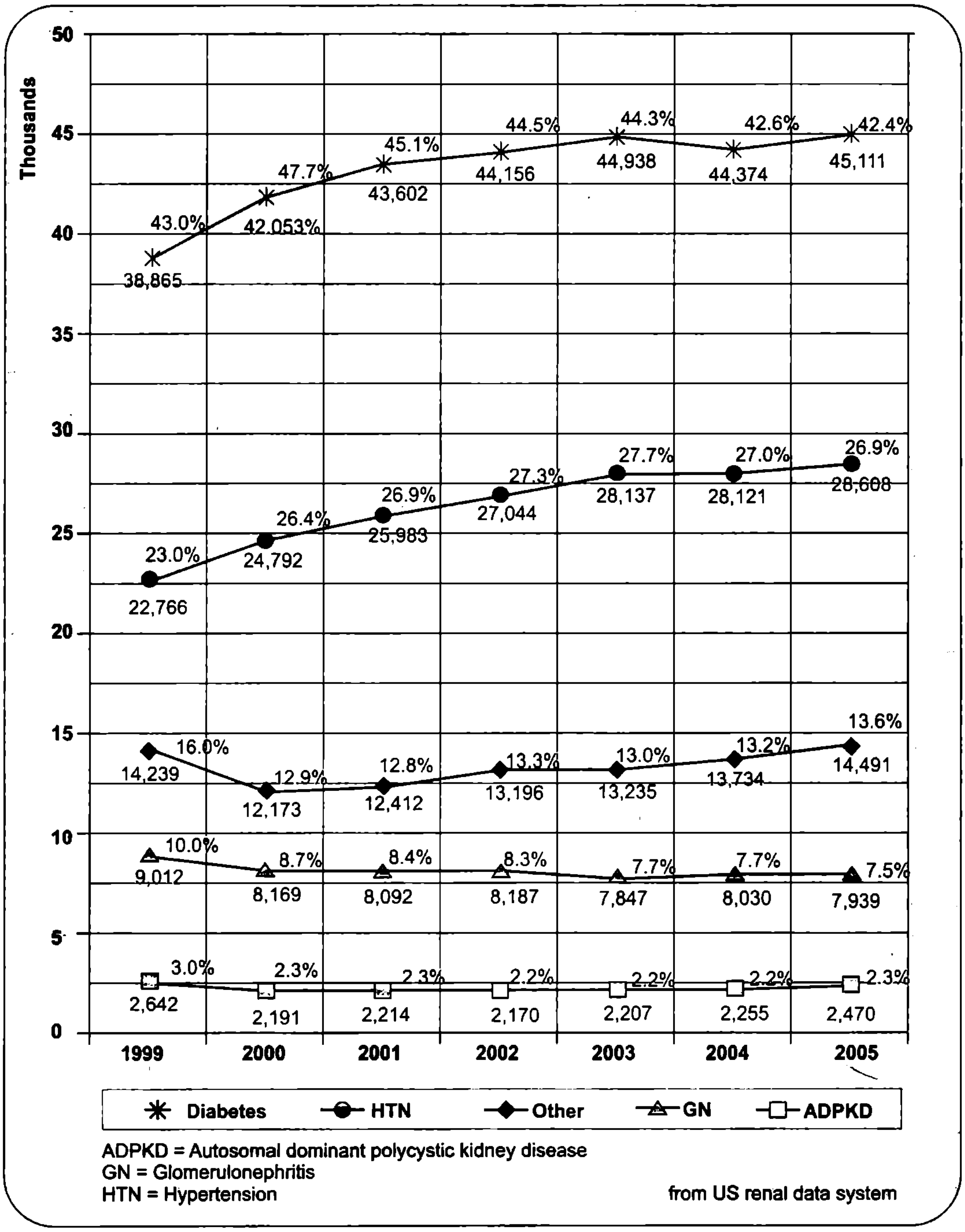
Table 2. Guidelines in treating hypertension in the elderly

1. Check for postural and postprandial hypotension before starting drug therapy.
2. Choose drugs that will help other concomitant conditions.
3. Start with small doses, titrating gradually.
4. Use longer acting, once daily formulations.
5. Avoid drug interactions, particularly from over-the-counter medications, e.g., nonsteroidal anti-inflammatory drugs.
6. Look for subtle drug-induced adverse effects, e.g., weakness, dizziness, depression, confusion.
7. Monitor home blood pressure to avoid over and under treatment.
8. Aim for the goal of systolic BP = 140-145, diastolic = 80-85.

Source: Adapted from Kaplan NM: Promises and perils of treating the elderly hypertensive. Am J Med Sci 1993;305: 183-97 with permission.

≥30 ml/min). The goal in those with reduced renal function is to prevent progression to ESRD (eGFR <15 ml/min).

A patient is presented here to exemplify just that. 70 years white male was first seen in author's office on March 17, 2008, with five years history of hypertension He already shows evidence of renal damage and coronary artery disease with coronary artery bypass graft surgery done in 1992. He was a smoker but quit in 1990. The history of coronary artery bypass graft suggests



ADPKD = Autosomal dominant polycystic kidney disease
GN = Glomerulonephritis
HTN = Hypertension

from US renal data system

Figure 1

hypertension longer than five years especially since he has no diabetes. Medication at the time of first office visit were amlopidine 5 mg per oral daily, furosemide 40 mg per oral daily, prednisone 10 mg per oral daily. The course of office visits is shown in Table 3.

His renal function rapidly deteriorated from 2006 to 2008 with rise of serum creatinine from 1.9 to 2.6 mg/dL due to uncontrolled hypertension. From 2009 until July 2010 his renal function is improved with sustained control of BP. He monitors his BP at home. All readings are normal. Therefore intensive hypertension control as in this patient illustrates that preservation of renal function with no progression to ESRD is not only a reality but an actuality provided BP is kept normal with appropriate therapy and sometimes adjuvant therapy such as sodium bicarbonate to combat metabolic acidosis, as in this patient.

Intensive BP control in the office setting is a prelude to preservation of renal function in patients with resistant hypertension and even after unilateral nephrectomy. The following patient illustrates that scenario. 72 years white male was referred to the author for uncontrolled hypertension in September 2002. His BP readings were 180/100 mmHg sitting and 220/110 mmHg standing despite three-line antihypertensive therapy consisting of fosinopril (Monopril•) 40 mg daily, candesartan (Atacand•) 32 mg + HCTZ 25 mg daily and metoprolol XL 200 mg daily. In an office visit in December 2002, his BP were sitting 180/110 standing 160 to 170/110.

His renal panel in August 2002 showed BUN/creatinine 26/1.7 mg/dL As of April 2001, his BUN/creatinine were 22/1.2. He lost 29.4 percent clearance in terms of serum creatinine increase. Atacand was

Table 3. Course of office visits

Date 2006-2010	*Symptoms*	*BP (mmHg) Sitting*	*BUN/SCr/eGFR (mg/dL/ml/min)*	*Serum K (mmol/L)*	*Hb (g/dL)*
2006/March 6		NA	21/1.9	4.3	13.5
2008/Jan 2		170/110	NA	NA	NA
March 17	Occasional shortness of breath	180/110	NA	NA	NA
		Δ Therapy 1. Amlodipine 5 mg twice daily 2. Added atenolol (Tenormin®) 50 mg daily 3. Reduce furosemide to 40 mg every other day 4. Reduce prednisone to 5 mg daily			
April 3	None	140/90	35/2.6/25	3.9	13.1
		24 h Ccl 30.5 ml/min	PRA 0.6 ng/ml/h Aldosterone 3 ng/dL		
		Prednisone d/c Δ furosemide Mon, Wed, Fri ↑ Amlodipine 10 mg per oral twice daily			
August 8	None	140/80	37/2.72/25	5.0	12
		Allopurinol 150 mg daily for hyperuricemia			
Dec 4	None	140/80	24/2.83/24	5.0	11.6
2009/Jan 5	None	140/80	33/2.55/27	4.7	12.2
		PO_2 90.1 mmHg, HCO_3 22.5 mmol/L Added Sodium bicarbonate 650 mg per oral TID			
May 28	None	140/70	24/2.27/29	4.3	12
Oct 28	None	130/80	25/2.11/31	4.4	12.1
2010/Jan 29	None	130/70	24/2.31/28	4.6	12.3
July 16	None	120/70	30/2.13/31	5.3*	13

SCr = serum creatinine, eGFR = estimated glomerular filtration rate, PRA = plasma renin activity, D/C = discontinued, NA = not available, Ccl = creatinine clearance.

* Excessive fruit consumption

discontinued. He was advised to continue fosinopril, metoprolol and HCTZ. His BP control improved and serum creatinine decreased to 1.5 mg/dL. Serum potassium increased to 5.1 mmol/L, when fosinopril was discontinued. He had an MRA of the kidneys done on October 8, 2002, which showed that the right kidney is shrinked. Right kidney had two renal arteries both showing stenosis greater than 50 percent. Left kidney and left renal artery were normal. Radiologist felt that radiological intervention such as angioplasty and stent placement would be most difficult and without benefit in the atrophic right kidney.

His antihypertensive regimen changed to minoxidil 5 mg twice daily, labetalol 100 mg TID, clonidine 0.2 mg TID, furosemide 40 mg daily. With this regimen, for the first time in an office visit on January 29, 2003, BP control markedly improved. They were sitting 130/80 mmHg and standing 110/90 mmHg. On December 12, 2002, his PRA was 0.79 ng/ml/hr and serum aldosterone level was 4.7 ng/dL. In no time his PRA was elevated. Although PRA was not elevated, atrophic right kidney was considered to be cause of his resistant hypertension. This thought prompted him to undergo right nephrectomy in December 2004 with a hope to secure good BP control. After nephrectomy, BP control improved with maximum doses of four lines antihypertensive therapy. These medications consist of hydroclorothiazide 25 mg once daily, amlodipine 10 mg twice daily, clonidine 0.2 mg twice daily and atenolol 100 mg twice daily. His BP control varied with periodic elevations such as March 14, 2007, office visit BP 150/90 mmHg sitting and 170/80 mmHg standing. Two years later on March 25 his BP were 160/82 mmHg sitting and 150/88 standing. However, over the years his BP control showed good improvement. For instance May 26, 2010, his BP were 150/80 mmHg sitting and 120/70 standing. Renal function followed the same pattern which is stable at a level of stage 3 chronic kidney disease but associated with periodically slight deterioration or improvement (Fig. 2).

Notwithstanding uncontrolled hypertension and unilateral nephrectomy his renal function decreased only slightly. Renal function parameters including BUN, serum creatinine and eGFR and hemoglobin over the years were analyzed for significant changes. There was no relationship between time and BUN, eGFR or hemoglobin. There is a relationship between time and serum creatinine. Overtime there is a slight but significant increase in serum creatinine from year to year (Fig. 2). The hemoglobin levels are shown in Figure 3. He did not require erythropoietic stimulating agent. He has remained stable at stage 3 CKD.

Therefore it is prudent to state that minimal deterioration of renal function over the years with no doubling of serum creatinine and no dialysis in this patient and the previous patient was granted by complete avoidance of ACEI/ARB drugs to control BP in both patients. Further hemoglobin has remained unchanged in parallel with essentially stable renal function, and again by avoiding use of ACEI/ARB drugs which cause anemia.

Caveats in the Antihypertensive Therapy

There are three caveats in antihypertensive therapy:

1. Symptomatic adverse effects
2. Asymptomatic metabolic disturbances
3. Withdrawal syndromes

Symptomatic Adverse Effects

There are many symptomatic adverse effects consisting of drowsiness, dry mouth, tiredness and decreased sense of well-being. These adverse effects do not dissatisfy a patient as much as sexual dysfunction or impotence does. The latter is a major cause of discontinuation of

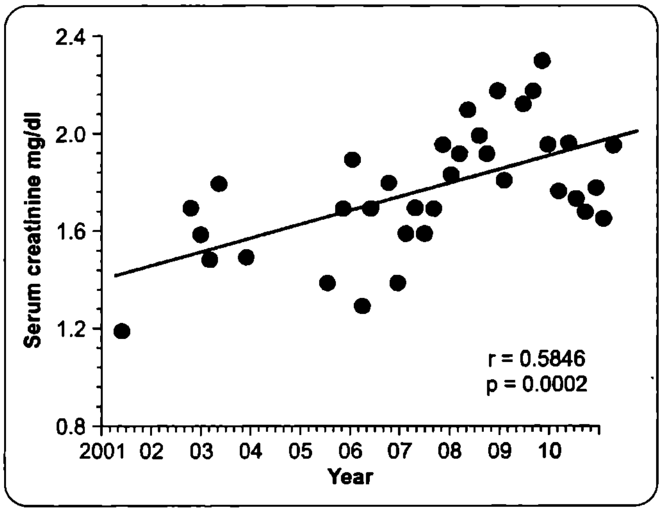


Figure 2: 72-year-old white male with single left kidney. Atrophic right kidney, he underwent right nephrectomy for hypertension control in 2004. There is a slight but significant increase of serum creatinine over a period of 10 years. Serum creatinine has remained less than 2.5 mg/dL throughout the entire period

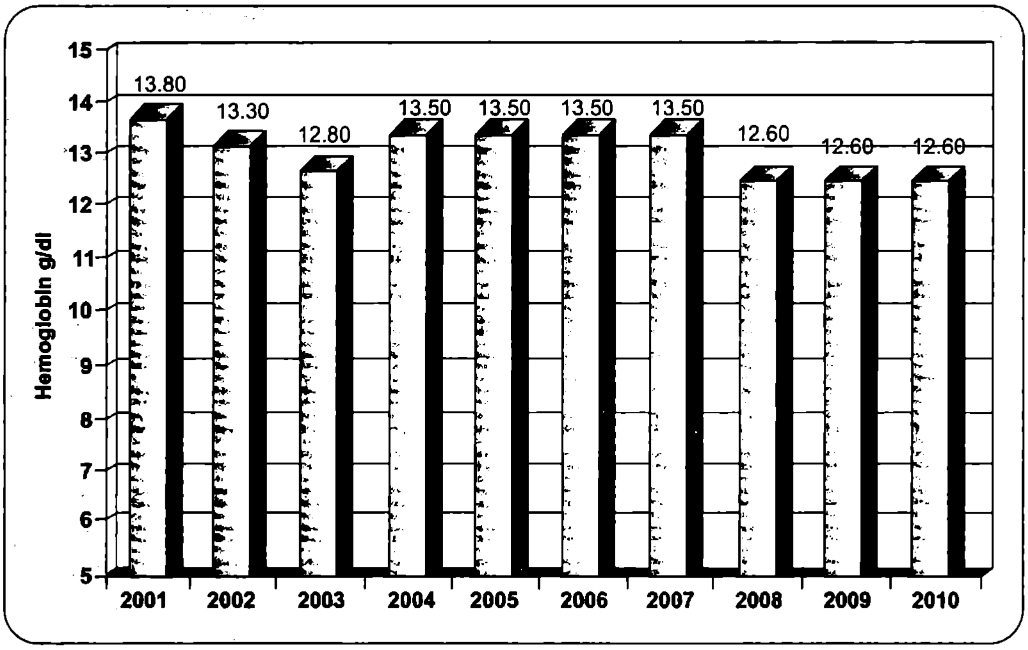


Figure 3: 72-year-old White Male: mean hemoglobin (g/dL) levels over the years not requiring erythropoietin stimulating agents. There is a slight but no significant change in hemoglobin level over 10 years period

therapy or noncompliance. Impotence is a very common complaint among the patients who receive a diuretic, a beta blocker, a central inhibitor or a combination of beta blocker or central inhibitor and a diuretic. Impotence is a less common complaint among patients treated with calcium channel blockers, ACE inhibitors or peripheral vasodilators.

The exact mechanism of impotence induced by thiazide diuretics is unclear. Urinary loss of zinc and hypozincemia has been proposed. Impotence produced by beta blockers and central inhibitors is due to blunted sympathetic drive which is necessary for penile erection. In addition, drowsiness or excessive sleepiness induced by these drugs further attenuate the ability to perform sexual intercourse in case of a male or participate in sexual intercourse in case of a female. The wives or significant others of male patients often come to the author with the complaint of impotence of their spouses or friends. Although the drug(s) in question have produced adequate control of BP, however, withdrawal of these drugs has become imperative for impotence. The antihypertensive potency of diuretics and central inhibitors. although is similar to calcium channel blockers or ACE inhibitors, and more importantly they are cheaper, but for the reason of impotence alone, they are less popular than calcium channel blockers or ACE inhibitors among the patients as well as their spouses or significant others.

Asymptomatic Metabolic Disturbances

The metabolic disturbances consist of impaired glucose tolerance (IGT), overt diabetes and insulin resistance. Although insulin resistance is increasingly reported, its relationship to hypertension is completely obscure. Insulin resistance has become a bargaining chip among the drug manufacturers to sell their product. Treatment with a thiazide diuretic, a beta-blocker, or a combination of both produces IGT. The incidence of IGT or diabetes is fivefold higher among patients treated with a monotherapy, and twelve-fold higher in patients treated with a combined therapy. The two beta-blockers metoprolol and atenolol, in daily doses of 200 mg and 50 mg, respectively, reduce insulin sensitivity by 20 and 13 percent, respectively. During treatment with a thiazide diuretic, insulin sensitivity is reduced by 11 percent. On the other hand, calcium channel blockers cause no significant change in insulin sensitivity. ACE inhibitors improve insulin sensitivity by 11 percent. Beta-blockers also increase serum triglyceride levels and reduce HDL cholesterol. It is highly disputed whether these lipid disturbances are independent risk factors. Insulin has been found to be a growth factor for VSMCs and elevated insulin levels are associated with enhanced reabsorption of Na^+ and water by the kidneys resulting in volume-dependent hypertension. The importance of insulin resistance as a primary risk factor has not been elucidated. Hyperuricemia is also common with diuretic therapy. However, it is controversial if this diuretic-induced hyperuricemia is detrimental and should that be treated.

Withdrawal Syndromes

Beta-blockers and central inhibitors blunt the sympathetic response especially during exercise and excitement. Thus these drugs not only decrease BP at rest, but also attenuate rise of BP during exercise, excitement or emotional outbursts. In addition, these drugs by reducing cardiac output decrease myocardial oxygen consumption and improve exercise tolerance in patients with angina. Therefore, sudden discontinuation of these drugs, which often happens due to impotence, could result in a sympathetic hyperactivity with rebound hypertension and stroke, or exacerbation of angina. Hence the patients and their families must be advised against sudden withdrawal or stoppage of these drugs. Should problems occur with the use of these drugs, the patients should immediately seek medical advice.

Hypertensive Emergencies

The incidence of malignant hypertension has progressively declined since 1960. There are two reasons for this declining incidence i) general public has become alerted to the dangers of untreated hypertension and is taking advantage of hypertension detection and treatment programs, and ii) increasing availability of a wide variety of antihypertensive drugs has helped to obtain more effective BP control now than in 1960s and prior to 1960. The introduction of hypertension detection and treatment programs in the United States of America has reached a milestone in the amelioration of hypertensive emergencies. For the past 20 years, occasional patients were admitted to the hospital where author is a consultant, with hypertensive emergency such as, hypertensive encephalopathy, acute CHF or threatened stroke, except those under specific conditions. These are i) Progressive systemic sclerosis; ii) Patients on maintenance hemodialysis. In these two situations, rapid increase of BP or persistently marked elevation of BP, accompanied by headache and sometimes nausea are not uncommon. These have been frequently considered as hypertensive urgencies rather than emergencies. These can be treated effectively by fast acting antihypertensive drugs given orally. These drugs include clonidine, captopril or labetalol. Clonidine 0.2 mg orally initially then 0.1 mg two hours later is very effective. Clonidine in particular, is very effective in lowering BP and ameliorating symptoms in African-Americans and dialysis patients. Captopril 25 mg crushed and mixed with water or sublingually can lower BP of 30 to 40 mmHg systolic and 20 to 30 mmHg diastolic within 30 minutes. Labetalol 100 to 200 mg given orally also lowers BP rather rapidly. In hypertensive emergencies manifested by encephalopathic picture intravenous administration of an antihypertensive drug is essential for prompt reduction of BP. Prompt reduction of BP will likely avert impending stroke, and facilitate control of CHF by reducing diastolic tension on the heart, The antihypertensive drugs that can be used parenterally to obtain rapid reduction of BP include sodium nitroprusside, hydralazine and labetalol. Their dosage, duration of action and side effects profile are present in Table 4.

The mechanism action of hydralazine, labetalol has been discussed. Sodium nitroprusside pharmacologically relaxes arteriolar and venous smooth muscle equally by interfering with both influx and the intracellular activation of calcium. It is metabolized by the liver and excreted by the kidneys. Cyanide and thiocyanate are both metabolic products of sodium nitroprusside metabolism. Thiocyanate, manifested as tinnitus, delirium or blurred vision, should be monitored.

Diagnosis and Management of High Blood Pressure in Special Situations

Hypertensive Patients Undergoing Surgery

Sudden increase of BP during surgery is not uncommon. This is more likely to occur in untreated or uncontrolled hypertensive than normotensive subjects because of stress. Rapid increase of BP in a hypertensive subject may lead to stroke. It has been shown that patients with hypertension whose BP has been controlled on medication(s) tolerate anesthesia better than those whose BP are poorly controlled. BP medication should be maintained on their regimen until the time of surgery, and therapy should be reinstated as soon as possible after surgery. If oral intake must be interrupted, parenteral therapy with hydralazine, nitroprusside, ACE inhibitors, such as enalapril may be used to prevent the rebound hypertension that may follow sudden discontinuation of central inhibitor. In all cases, anesthesiologists must be aware of the patient's medication lists.

Renovascular Hypertension

Rapid onset of hypertension in a normotensive adult, difficult to control BP with three or four line therapy or sudden decrease of renal function in a hypertensive individual arouses the suspicion of renovascular hypertension. Details of the diagnoses and management will be found in the chapter on renovascular disease.

Hypertension with Hypokalemia

Hypokalemia in a hypertensive patient is most commonly due to the use of a diuretic, thiazide or loop diuretic. The absence of history of diuretic use, laxative abuse, diarrhea, vomiting in a hypertensive patient who has hypokalemia signifies primary or secondary hyperaldosteronism. Severe hypokalemia in a hypertensive patient but not treated with a diuretic strongly suggests primary hyperaldosteronism due to an aldosterone secreting tumor. A patient is presented here to illustrate that scenario.

BW, a 65-year-old African-American female was referred to the author for consultation with a long history of hypokalemia and hypertension. She denies history of diuretic or laxative intake. She is active and reliable. Her serial serum potassium levels prior to the office visit are shown in Table 5.

These elevated glucose levels are most likely due to hypokalemia since correction of hypokalemia resulted in normalization of blood glucose levels (Table 6).

She was hypertensive with BP 160 mmHg systolic and 104 mmHg diastolic. She was receiving amlodipine 5 mg daily. She was advised low salt diet and spironolactone

Table 4. Parenteral drugs for treatment of hypertensive emergencies

	Dose	*Onset of Action*	*Adverse Reactions*
Vasodilators Sodium nitroprusside	0.3-5 ug/kg/min as IV infusion	Immediate	Nausea, vomiting, muscle twitching, thiocyanate intoxication, methemoglobinemia
Hydralazine	5-10 mg IV bolus, repeat 5-10 mg IV 15-20 min later, 10-50 mg/IM	10 min 20-30 min 20-30	Tachycardia, headache, vomiting, aggravation of angina pectoris
Labetalol	200 mg/200 ml of 5% dextrose to make 1 mg/ml per min IV infusion or 20-40 mg direct IV bolus. 40 mg IV bolus may be repeated at 10-20 min	5-15 min	Hypotension, bronchospasm

Table 5. Serial serum potassium levels

Date	*Potassium (mEq/L)*	*Sodium (mEq/L)*	*Glucose (mg/dl)*	*Creatinine (mg/dl)*
Aug 6, 1996	3.2	NA	NA	NA
Jan 13, 1998	3.2	144	126$^+$	1.0
Jan 5, 1999	3.1			
Jan 9, 1999	3.5			
Feb 4, 2000	3.4	144	155+	0.9
May 30, 2000	3.1	144		
May 30, 2000	Urinary potassium 22 mEq/L			
Creatinine clearance = 67 ml/min		$^+$elevated		
NA = not available.				

Table 6. Blood pressure and serum chemistry values

Date	*Blood Pressure (mmHg)*	*Potassium (mEq/L)*	*Sodium (mEq/L)*	*Glucose (mg/dl)*	*Creatinine (mg/dl)*
June 29, 00	160/104				
July 03, 00			Spironolactone 25 mg per oral TID initiated		
July 27, 00	140/48	4.6	143	108	1/..2
			Spironolactone 25 mg per oral BID		
Dec 13, 00	140/80	3.5	147	116	0.7
Feb 02, 01	150/100	4.1	143	115	0.8
			Amlodipine 5 mg BID, Spironolactone 25 mg TID		
June 05, 01	130/70	3.9	145	110	0.9

25 mg TID after blood samples were obtained for plasma renin and aldosterone levels. Her renin was 0.79 ng/ml/h (N = 1.3 to 3.95 ng/ml/h) and aldosterone 13.4 ng/dl (N = 1.0 to 15.0 ng/dl). Abdominal CT scan and MRI have shown a finding consistent with right adrenal adenoma. Her BP and serum potassium are normal with spironolactone. Over the years her BP and serum potassium are normal with amlodipine and spironolactone. Adrenal adenoma has remained unchanged.

Hypertension Associated with Oral Contraceptives

An appreciable number of women taking oral contraceptives experience a small but detectable increase in both SBP and DBP, usually within the normal range. Hypertension has been reported to be two to three times more common in women taking oral contraceptives for five years or longer than those not taking oral contraceptives. Smoking aggravates oral contraceptives induced hypertension. Therefore woman taking oral contraceptives must refrain from smoking. Due to dose adjustment of estrogen and progesterone in the contraceptive preparations of current use, the current incidence of oral contraceptive induced hypertension is less than reported earlier.

The mechanism of hypertension is unclear; however, renin-dependent or volume dependent hypertension remains a possibility. Abstinence from the pill and the use of other contraceptive methods for protection against pregnancy are the most affordable advice for amelioration of contraceptive-induced hypertension. If pill must continue because other contraceptive devices cannot be used, antihypertensive drugs and dietary restriction of salt should be instituted to keep BP under control.

Hypertension in Pregnancy

See chapter on Hypertension in Pregnancy.

KEY POINTS

1. The objectives of treating hypertensive patients are to achieve adequate control of BP and adhere to this adequate control on a long-term basis.
2. Adequate control of BP means systolic less than 140 and diastolic less than 80 mmHg. The maintenance of adequate control of BP most likely will prevent stroke, or heart attack and heart failure.
3. Adequate control of BP also is likely to cause regression of LV hypertrophy and quite likely preserve or improve renal function. The last two salutary effects combined will further reduce the morbidity and mortality in the hypertensive subjects.
4. Choice of antihypertensive drugs is very important, so that our efforts to control hypertension do not grossly alter the quality of life. The cost of the drugs is also a factor. Thus, thiazide diuretics, beta-blockers and central inhibitors that are relatively inexpensive and adequately lower BP should be a common choice. However, if drowsiness interferes with work or impotence becomes a threat for the marital partner or significant other, adjustment has to be made.
5. The metabolic abnormalities induced by these relatively inexpensive drugs have put calcium channel blocker and ACE inhibitor group of drugs on the top of antihypertensive therapy. They are far

more expensive; yet offer no greater anti-hypertensive advantage than a diuretic or clonidine except in special circumstances.

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Pregnancy-related Renal Diseases and Hypertension

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INTRODUCTION

Pregnancy is associated with several physiological and hemodynamic changes. The kidney can be influenced by these changes as well as by certain pathological alterations which can occur during pregnancy. A clear understanding of these alterations is essential for the diagnosis and management of pregnancy related renal disease and hypertension.

The maternal changes start from the time of fertilization and continue throughout pregnancy and reverse almost completely to the pre-pregnant state within six to eight weeks of delivery. A pregnant woman gains approximately 12 to 14 kilograms of weight and is mainly contributed by retention of water distributed in the fetus, amniotic fluid, uteroplacental unit and maternal tissues. The weight gain is proportionally more during the second and third trimsters. Other factors contributing to weight gain include weight of the fetoplacental unit, maternal fat accumulation and increase in the uterine musculature. A pregnant woman also retains nearly 1,000 mEq of sodium and 350 mEq of potassium. Due to the accumulation of nearly seven liters of water, the levels of plasma proteins, sodium, potassium and osmolality decrease by approximately 3 percent. The resting heart rate increases by 10 beats per minute. Cardiac output and stroke volume are the highest when the woman remains in left lateral recumbency. Significant changes also occur in the structure and function of the urinary system in the course of a normal pregnancy. The increase in renal size of up to 1 cm is due to an increase in the renal parenchymal volume and water content. Ureteric peristalsis decreases by third month and dilatation of the pelvicalyceal system and ureters are noted in nearly 90 percent of women in the last trimester. The right ureter is more dilated than the left and the dilatation generally ceases at the pelvic brim. The mechanical theory postulates that pressure by the enlarged uterus on the ureter, and pressure from the dilated ovarian vein or iliac artery crossing the ureter at about the level of pelvic brim, causes dilatation of the ureter. A filling defect may be seen in the dilated ureter in intravenous urogram at the site of crossing of the iliac artery. This is called the "iliac sign". The hormonal theory suggests that different hormones acting on the smooth muscles of the pelvicalyceal system cause ureteral dilatation. In preeclampsia (PE), since blood flow to the placenta may be impaired, ureteric dilatation is also less frequent. Increased volume of residual urine in the urinary tract and a possible reduction in peristalsis may predispose to development of urinary tract infections.

Renal plasma flow increases by nearly 70 percent in early pregnancy and stabilizes at 50 to 60 percent during the third trimester. The glomerular filtration rates (GFR) starts to increase by the first month after conception, reaches 50 percent in midpregnancy and returns to pre-pregnant levels near term. As a result of the increase in GFR, blood urea, serum creatinine and serum uric acid levels are lower than nonpregnant levels throughout normal pregnancy. Since the filtered load is high, the urinary excretion of amino acids, water-soluble vitamins, proteins and glucose are increased during normal pregnancy.

Normal Blood Pressure Changes and Criteria for Diagnosis of Hypertension

A great deal of advancement has taken place in our understanding of the blood pressure (BP) variations in normal pregnancy. Blood volume and cardiac output are markedly increased by almost 50 percent during pregnancy. In addition, levels of renin substrate, renin, angiotensin I and angiotensin II are increased. In spite of this, the BP tends to fall. The uteroplacental unit which acts as a low resistance shunt leads to reduced vascular resistance. The cutaneous and renal circulations also contribute to the overall reduction in the peripheral vascular resistance. An increase in vasodilator prostaglandins or increase in angiotensinase enzymes may be responsible for neutralizing the effect of angiotensin II. Normal pregnant women do not respond to the pressor effect of exogenous angiotensin II. This may be due to increased level of endogenous angiotensin II and saturation of the receptors. An increased output of endothelium derived relaxing factor (nitric oxide) has been implicated for decreasing angiotensin II sensitivity. During early pregnancy, systolic and diastolic pressures are lower than pre-pregnant levels and the fall reaches a nadir by midpregnancy. Thereafter, it rises towards pre-pregnant levels at full term.

As there is no clear-cut dividing line between normal and abnormal BP during pregnancy, certain arbitrary BP levels have been established for clinical purposes. The Committee on Terminology of the American College of Obstetricians and Gynecologists suggested any one of the following criteria for the diagnosis of hypertension in pregnant women.

1. A sustained rise of 30 mmHg or more in systolic BP;
2. A sustained rise of 15 mmHg or more in diastolic BP;
3. A sustained systolic BP of 140 mmHg or more and;
4. A sustained diastolic BP of 90 mmHg or more.

"Sustained" refers to elevated BP observed on two different occasions, at least six hours apart.

These criteria have been largely abandoned because of the considerable variability of BP in normal women. In addition, to apply the above criteria, the BP in the prepregnant state or soon after conception must be known. Since these BP readings are often not available, the diagnosis of pregnancy-induced hypertension (PIH) becomes difficult. To overcome this difficulty, Lindheimer has suggested the upper limit of normal diastolic BP in pregnancy to be 75 mmHg in midtrimester and 85 mmHg in last trimester. A threshold diastolic BP of 90 mm Hg together with an increase of 25 mm Hg has also been suggested to improve the diagnosis.

HYPERTENSIVE DISEASES IN PREGNANCY

The most accepted clinical classification of the hypertensive disorders of pregnancy is that recommended by the Committee of the American College of Obstetricians and Gynecologists. This classification is presented in Table 1.

Preeclampsia

PE is characterized by a constellation of signs and symptoms including new onset of hypertension, proteinuria, often with edema and occasionally complicated by coagulation and liver function abnormalities. Hypertension occurs after 20 weeks of pregnancy. PE/eclampsia is a disease peculiar to pregnancy and was considered as one of the "toxemias" of pregnancy but the term toxemia is no longer used because no toxins have been identified in these women. The term PE, however, is used synonymously with PIH. Incidence of PE is estimated to range from 3 to 10 percent of all pregnancies. There are a number of predisposing factors for the development of PE. Higher incidence has been observed in women who are primigravida, extremes of age, multiple pregnancy, hydatidiform mole, diabetes, polyhydramnios, fetal anomalies, hydrops fetalis and family history of PE/eclampsia.

Chronic Hypertension of Whatever Cause

This group includes those patients with essential or secondary hypertension who subsequently become pregnant. Those who have hypertension before twenty weeks of pregnancy are more likely to fall into this group.

Table 1. Hypertensive disorders of pregnancy

1. Pregnancy-induced hypertension (preeclampsia/eclampsia).
2. Chronic hypertension of whatever cause.
3. Chronic hypertension with superimposed preeclamspia.
4. Late or "transient" hypertension.

Chronic Hypertension with Super-imposed Preeclampsia

Almost three quarters of those with chronic hypertension develop superimposed PE in the second half of pregnancy. PE in this group is often more severe. Chronic hypertensive disease is independently associated with an increased incidence of not only PE but also gestational diabetes and placental abruption.

Late or Transient Hypertension

This group includes those who develop hypertension in the last trimester or immediate postpartum which normalizes by the tenth postpartum day.

PATHOPHYSIOLOGY OF PREECLAMPSIA/ECLAMPSIA

PIH is a multisystem disease characterized by vascular endothelial damage and dysfunction. There have been various postulates on its pathogenesis including the role of superficial placentation, immune maladaptation and reduced angiogenic factors. The placenta rather than the fetus seems to have a role in the pathogenesis of PE/eclampsia since it occurs in situations when the placenta is present but fetus is absent (e.g., hydatidiform mole). The placenta shows evidence of hypoperfusion and ischemia with scars. Normally, during pregnancy, the decidual part of spiral arteries invaded by the cytotrophoblast and replaced with fibrinoid material which transforms the vascular supply from a high pressure, low flow system to a low pressure, high flow system. This helps to meet the needs of the fetus and placenta. The loss of endothelium and muscle layer results in failure of the blood vessels to respond to vasomotor stimuli. In contrast, in PIH, the trophoblastic invasion is partially impaired. and preservation of the muscle layers makes the vessel sensitive to vasomotor stimuli resulting in reduced placental blood flow. The trophoblastic invasion of spiral arteries and remodeling of the vasculature in normal pregnancy are favored by angiogenic proteins produced by the normal placenta like vascular endothelial growth factor (VEGF) and placental growth factor (PlGF). The receptor for these growth factors is called fms like tyrosine kinase (Flt1) which exists in two forms, a membrane bound form and a soluble secreted form (sFlt1). An excess of sFlt1 occurs in PE. This can bind to circulating VEGF and PlGF and can affect their binding to the endothelium receptors. This can result in a generalized endothelial damage and multiorgan involvement. Thus the endothelial damage which started in the placenta becomes generalized. The defective trophoblastic invasion may be due to the excess sFlt1 though various other antiangiogenic factors are also postulated. Asymmetric dimethyl arginine (ADMA), an endogenous endothelial nitric oxide synthase inhibitor may have a role. A decrease in nitric oxide, prostacyclin and release of procoagulant proteins like von Willebrand factor, endothelin, fibronectin and thrombomodulin may also have a role.

Plasma volume was found to be significantly decreased in patients with PIH compared to pregnant women with normal BP. The lowest intravascular volumes were found in pregnant women who developed severe PIH and evidence of uteroplacental insufficiency. Despite contracted plasma volume, women with PE are characterized by relatively greater BP sensitivity to exogenous Angiotensin II than normotensive pregnant women. Evidence suggests that this is due to an alteration in angiotensin II receptor sites.

Thromboxane A2 production is more in those having more severe forms of preeclampsia and coagulopathy. Low-dose aspirin selectively inhibits the synthesis of platelet thromboxane by acting on the cyclooxygenase enzyme without affecting the production of endothelium-derived prostacyclin or nitric oxide. This may be the basis for the beneficial role of low-dose aspirin in some cases of PE. Oxidative stress may also have a role with increased levels of reactive oxidation species being detected in PE. This may suggest a role for antioxidants.

The salient pathological changes in the kidneys include enlargement of the glomeruli with no increase in the number of cells. The endothelial cells are swollen and fill up the capillary loops. These changes have been termed "glomerular endotheliosis".

Diagnosis

PE can be suspected clinically by noting BP elevation which may be associated with headache, epigastric or right upper quadrant abdominal pain, visual abnormalities such as scotoma and cortical blindness. Visual disturbances are due to spasm of retinal arterioles and suggest generalized increase in vascular tone. Symptoms like epigastric discomfort and visual disturbances may precede the development of generalized convulsions.

If convulsions occur, the diagnosis is eclampsia. Fifty percent of cases of eclampsia occur before labor, 25 percent during labor and 25 percent in the postpartum period. Severe dysfunction of pulmonary, renal, hepatic and central nervous systems may occur.

Some laboratory parameters may be helpful in the diagnosis. Examination of urine reveals proteinuria which may be heavy even in the nephrotic range, and nonselective with excretion of high molecular weight proteins. The urinary sediment is generally unremarkable but may show only granular casts. Presence of red blood cells, red blood cell casts or other findings suggestive of nephritic illness indicates undetected preexisting renal diseases. The important hematologic abnormalities are increased hematocrit and hemoglobin due to reduction of plasma volume, thrombocytopenia and increased thrombin time. Blood levels of aspartate aminotransferase, alanine aminotransferase and lactic dehydrogenase enzymes may be elevated, but they return to normal within 10 days of delivery. Renal function may be decreased with elevation of blood urea nitrogen (BUN) and serum creatinine. Due to the marked increase in GFR, BUN and serum creatinine levels are much lower in pregnant compared to nonpregnant women. The normal levels of urea nitrogen in nonpregnant and pregnant women are 10 to 16 mg/dL and 5 to 8 mg/dL, respectively. The corresponding normal values of serum creatinine are 0.8 to 0.9 mg/dL and 0.4 mg/dL respectively. Therefore if BUN and serum creatinine during pregnancy are at or above the pre-pregnant levels, it indicates impairment of GFR. Similarly, serum uric acid is low (2.5 mg/dL) due to enhanced GFR. Elevation of serum uric acid to 4.5 mg/dL is an indication of enhanced proximal tubular reabsorption of uric acid caused by volume contraction and consequently decreased GFR. Hyperuricemia is of diagnostic importance, as it helps to distinguish women with PIH from those with chronic hypertension. There is a postulate that the hyperuricemia could independently contribute to the hypertension. Intrauterine growth retardation can be quantified by serially monitoring the fetal growth clinically and by ultrasound scan.

It may be difficult to differentiate between preeclampisa and chronic hypertension complicating pregnancy. Presence of hypertension before conception or detection of hypertension before 20 weeks of gestation is not suggestive of PE. However, new onset of hypertension early in pregnancy, especially in primigravida signifies PE. Severe PE is invariably associated with hypertension but uncommon in multiparous women. The BP usually decreases dramatically following termination of pregnancy in PE. Severe PE may be confused with acute fatty liver of pregnancy, thrombotic microangiopathy, glomerulonephritis or systemic lupus erythematosus. A combination of development of hypertension during pregnancy, proteinuria and elevated serum uric acid supports a diagnosis of preeclampisa. Although the onset of hypertension frequently is abrupt and rapidly progressive, the mean BP of women destined to develop PE is higher in the first and second trimesters than the mean BP of those who do not develop PE.

Management

An important step in prevention of PE is to avoid teenage pregnancy or consider first pregnancy after the age of 35 years. In the antenatal checkup, care is taken to restrict maternal weight gain to less than 12.5 kg, and to avoid aggressive salt restriction or diuretic therapy. The preeclamptic women is hospitalized early and encouraged to rest on the left lateral position. Fetal growth parameters are monitored clinically and by ultrasound scans. The fetal prognosis has improved considerably by judicious and deliberate preterm delivery combined with the skill of the neonatologist and a good premature nursery. Doppler flow velocimetry has been used to monitor abnormalities in uterine and umbilical circulation. Calculation of the systolic/diastolic ratio of the uterine or umbilical artery provides an indirect evidence of the impedance of these circulations. A first stage test with uterine Doppler ultrasound at 20 to 24 weeks of gestation followed by a second stage test with ambulatory 24-hour BP monitoring in patients with abnormal uterine Doppler might indicate women at risk of developing PIH. The Doppler flow study should be repeated once at 32 to 34 weeks. If umbilical artery flow remains abnormal, attention should be focused on the fetus using ultrasonography to evaluate the possibility of chromosomal abnormalities, fetal growth assessment, fetal heart rate monitoring and the biophysical profile for development of hypoxia. Absent or reversed diastolic flow is an indication for daily fetal surveillance. The presence of any sign of fetal hypoxia should warrant delivery.

Depending on the facilities in the premature baby unit, labor is induced when the fetal weight is 1.5 to

1.8 kg, since the infant has more chances of survival in a good premature nursery than the womb of a mother with uncontrolled hypertension. It is suggested that delivery can be planned by 37th week in mild cases and by 34th week in more severe cases. Treatment should be instituted if diastolic BP is 85 mmHg in mid-pregnancy and 95 mmHg in late pregnancy. BP above 95 mmHg in mid-pregnancy or 100 mmHg in late pregnancy should be considered an emergency. If the fetal maturity and weight are satisfactory at the time of detection of hypertension, labor may be induced. Great caution must be exercised in prescribing antihypertensive drugs to hypertensive pregnant women. While centrally acting alpha-2 receptor agonists (methyldopa), vasodilators (hydralazine), beta-blockers (atenolol), combined alpha-beta receptor blocking agents (labetalol) and calcium channel blockers (nifedipine) are safe, other antihypertensive drugs such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists are unsafe. There is a great deal of controversy about the use of diuretics in PIH.

Centrally Acting Alpha-2 Receptor Agonists

Methyldopa, has been used most extensively for the control of BP during pregnancy. It is safe and effective, but may cause transient BP fall in the neonate. The dose is titrated depending on the response in individual cases. A dose of up to 4 gm per day can be given.

Vasodilators

Hydralazine is a vasodilator antihypertensive drug and can be used alone or in combination with methyldopa. It is quite safe but may produce transient tachycardia in the infant. It improves the uteroplacental circulation. It can be used intravenously in emergency. The usual oral dose is 50 mg four times daily. This drug is relatively less expensive and can be used as the first-line drug. It may produce headache and tachycardia in some patients.

Beta-Blockers

Beta-blockers were initially condemned because of fetal growth retardation, persistent neonatal hypoglycemia, respiratory depression and bradycardia. Studies have also noted poor development of the spiral arteries and intrauterine growth retardation. However, with careful use, beta-blockers such as atenolol and oxprenolol have been found to be effective during the latter part of pregnancy.

Combined Alpha-Beta Receptor Blockers

Labetalol belongs to this group and is being increasingly used in the management of hypertension in pregnancy in a dose of 100 to 200 mg orally twice daily. It has a number of advantages like insignificant maternal and fetal side effects, improved fetal lung maturity and improved uteroplacental circulation. A total dose up to 1,200 mg orally per day can be given. Some studies have noted an increase in retroplacental clots in a few cases. This drug is beneficial for the treatment of severely elevated BP or resistant hypertension during pregnancy.

Calcium Channel Blockers

Among the calcium channel blocking drugs, only nifedipine has been used successfully. Nifedipine 10 to 20 mg orally three to four times daily lowers BP in patients with severe hypertension during pregnancy and may be even preferable to hydralazine. Nifedipine has been used successfully to postpone delivery in patients with preterm labor. We have observed that in some women on nifedipine therapy, induction of labor with pitocin is attenuated or fails and uterine contraction is not satisfactory after cesarean section. If nifedipine is discontinued 48 to 72 hours prior to the induction of labor or cesarean section, uterine inhibition is reversed (unpublished personal observation). Although nifedipine has been used to prevent preterm labor, it does not arrest the process of labor once it is well established. Diltiazem can decrease proteinuria and can be used in patients with renal disease, hypertension and pregnancy.

Diazoxide

Diazoxide is a parenteral vasodilator agent used in emergencies. When given in bolus doses of 300 mg, it produces uterine atony. Therefore, small repeated doses are generally recommended. Since nifedipine can bring about rapid reduction of BP when given through the buccal route, intravenous diazoxide is not commonly used now.

Other Drugs

Alpha-receptor blocking agents such as prazosin, central alpha agonists such as clonidine, ACE inhibitors and angiotensin II receptor blockers like losartan are not recommended. Oligohydramnios and neonatal renal failure has been reported in a premature infant whose mother received enalapril in 32 to 35 weeks of her pregnancy.

Diuretics

As mentioned earlier, prevailing controversies are deterrent to the use of diuretics in the treatment of hypertension during pregnancy. Based on available data, it may be safer to control hypertension in pregnancy with other antihypertensive drugs and using diuretics judiciously in resistant cases with edema. In case of hypertensive emergency, intravenous or intramuscular hydralazine, methyldopa or diazoxide may be used. However, oral Labetalol or Nifedipine also act quickly. Sodium nitroprusside is not generally recommended since thiocyanate blood levels increase causing cyanide toxicity and reduced placental blood flow. It may be employed only if the mother's life is at risk or fetal outcome is inconsequential.

Once PE is confirmed, the expectant mother is hospitalized and severity is assessed as mild, moderate or severe. In mild and moderate cases, termination of pregnancy is recommended if pregnancy is close to term (36 weeks or later) and fetal maturity is acceptable. If the period of gestation is less than 36 weeks, the mother is closely observed and parameters like BP, urine output, proteinuria, optic fundi, neurologic status, BUN, serum creatinine, serum uric acid, lactic dehydrogenase, platelet count and aspartate aminotransferase are monitored. Fetal lung maturation can be assessed by determination of lecithin/sphingomyelin ratio or phosphatidylglycerol in the amniotic fluid. However, since the decision to deliver the baby preterm depends on maternal deterioration, this test should not be performed routinely. A favorable fetal lung maturity can help in a decision to terminate pregnancy earlier than 36 weeks with good results.

Under careful observation, the mother and fetus can continue to coexist with benefit to the fetus and relatively slight risk of immediate or remote harm to the mother. The maternal health and fetal growth are closely monitored, and a judicious and deliberate preterm delivery is conducted, if the fetus is viable and the maternal environment is hostile for further growth of the fetus. The presence of chorionic villi in some women incites development of vasospasm and hypertension which revert to normal following the expulsion/removal of the chorionic villi.

If the welfare of the mother is at risk and the fetus is severely growth retarded, or the mother has imminent eclampsia or convulsions, immediate termination of pregnancy remains the only alternative.

Treatment

In the event of development of eclampsia, the main objectives of treatment are the following:

Arrest/Prevent Convulsions

Early detection of hypertension and adequate control of BP with antihypertensive drugs can prevent development of eclampsia. Convulsions can be arrested and further occurrence is prevented by the timely use of parenteral magnesium sulfate. It can also decrease risk of eclampsia by more than half. The usual protocol followed is as follows: 20 ml solution of 20 percent magnesium sulfate ($MgSO_4$, $/7H_2O$, 4 gms) is given intravenously in five minutes followed by 10 ml solution of 50 percent magnesium sulfate given by deep intramuscular injection into each buttock (total = 10 gm intramuscularly). The convulsions are usually arrested by this regime. Subsequently, the patient is closely monitored for patellar jerk, urine flow rate and respirations. The loss of patellar jerk is the earliest warning sign of impending magnesium toxicity. If the patellar jerk is present, urine output is more than 100 ml in the previous four hours and respirations are adequate, a further dose of 10 ml 50 percent magnesium sulfate (5 gm) is administered into alternate buttocks every four hours. Administered in the above fashion, the plasma magnesium often increases to 7 to 9 mEq/L but stabilizes at a serum level of 4 to 7 mEq/L. Administration of magnesium sulfate is often continued for 24 hours postpartum.

Magnesium sulfate potentiates the hypotensive action of calcium channel blockers. It is believed to act at the neuromuscular junction. A comparative study between magnesium and phenytoin showed a better efficacy with the former. Magnesium toxicity can be counteracted by intravenous calcium administration.

Long-term use of diazepam as an anticonvulsant is not favorable for the fetus, since it may cause hypotonia, drowsiness and apnea for several hours after birth. The Apgar score may also be low. However, diazepam can be used to terminate a fit. The generalized central nervous system depression of mother and fetus discourages the use of morphine in this condition.

Terminate Pregnancy with Least Amount of Trauma to Mother and Fetus

In most cases, the termination of pregnancy can be easily accomplished by the use of oxytocin, 10 units in 250 ml of 5 percent dextrose in water as a controlled infusion.

Deliver an Infant Who may Subsequently Thrive

If the maternal health is not jeopardized, pregnancy may be continued under close monitoring of maternal and fetal parameters until the fetus is sufficiently mature to survive in the premature nursery.

Restore Mother's Health Completely

This requires close monitoring of the mother, particularly the BP during puerperium. Clinicians often make a mistake by abruptly stopping all drugs immediately after delivery or shortly thereafter. The mother may require a variable dose of antihypertnesive drugs for a few weeks. All cases of hypertension in pregnancy are not PE. Cases with undetected renal disease or essential hypertension may not come back for observation and diagnosis of hypertension is made for the first time during pregnancy. It is likely that such mothers need long-term administration of antihypertensive drugs.

Prognosis and Predictability

The long term prognosis of PE is controversial, particularly because the clinical diagnosis of PE may be confused with latent hypertension, preexisting renal disease or essential hypertension. Women with essential hypertension may have a significant fall of BP during pregnancy and may remain in the "normotensive" range throughout most of the pregnancy. Women with recurrent gestational hypertension should be considered to have preexisting hypertensive disease.

Pregnancy is now thought to act as a stress test and those who develop PE may be predisposed to endothelial injury and have an eightfold increased risk of cardiovascular disorders as well as hypertension and stroke in later life. They could also have an increased risk of dyslipidemia, insulin resistance and mortality, besides anemia and lung diseases. They should hence be advised lifestyle changes to decrease this risk. Those with recurrent hypertension or when hypertension occurs before 30 weeks may also have an increased incidence of subsequent chronic hypertension. It has been noted that if hypertension persists on the tenth postpartum day, the possibility of recurrence is higher. If the average systolic BP is more than 160 mmHg, the probability of recurrence is higher.

Roll-over test is a simple but nonspecific noninvasive test performed between 28 to 32 weeks. It can be used to detect patients at risk, since it has a higher negative predictive value. The BP is recorded 15 minutes after the subject assumes lateral recumbent posture or until the recordings are stable. Then the subject rolls over to a supine position and BP is checked after one minute. Any increase in diastolic BP of more than 20 mmHg is considered as positive. The gold standard in predicting those who are likely to develop PE in later pregnancy is the angiotensin infusion test based on the increased sensitivity to angiotensin. Antiplatelet agents would be expected to have theoretical advantage in view of the generalized endothelial damage. Low-dose aspirin was found to be beneficial in several initial trials. However, the optimism has been moderated following large scale randomized trials where a statistically significant reduction is hypertension and fetal morbidity and mortality was not seen. It would need to treat almost 90 patients with aspirin to prevent one case of PE. Thus, while aspirin may have a role in high-risk individuals, it cannot be recommended as routine prophylaxis. The following guidelines may be used for selecting pregnant women for low dose aspirin therapy:

1. Positive family history of PIH.
2. Previous history of PE.
3. Teenage pregnancy and pregnancy after 35 years.
4. Preexisting renal disease with hypertension.
5. Multiple pregnancy.
6. Rh negative mother.
7. Diabetic mother.
8. Positive roll-over test.
9. Positive AII infusion test.

Calcium supplementation was reported to be useful in preventing eclampsia, but subsequent trials did not reveal any significant beneficial effects.

The syndrome of hemolysis, elevated liver enzymes and thrombocytopenia (HELLP) has been recognized as a complication of PE for many years. This complicates 0.1 percent of pregnancies and could be associated with eclampsia. Most patients (90 percent) give a history of malaise for a few days prior to presentation. Nausea or vomiting and right upper quadrant pain are also common. Renal dysfunction is common. The typical hepatic lesion associated with HELLP syndrome is periportal or focal parenchymal necrosis, in which large hyaline deposits of fibrin-like materials can be seen in the sinusoids. Prompt delivery is advised, usually within 24 hours of the diagnosis.

ACUTE RENAL FAILURE IN PREGNANCY

Acute renal failure (ARF) is becoming an increasingly rare complication of pregnancy in industrialized countries because of a decrease in illicit abortions, improved prenatal care, and better management of maternal complications potentially leading to ARF. In the developing countries also, the occurrence of obstetric ARF is progressively declining in parallel to the improvement of social and economic status. The incidence of ARF in pregnancy has a bimodal pattern. During the first trimester, illegal abortion practices induced by crude methods like use of phenol, soap, quinine, other nephrotoxic abortifacients or introduction of foreign bodies into the uterine cavity result in sepsis (septic abortion) and ARF. Other factors like dehydration and shock due to hyperemesis gravidarum, bleeding, urinary infection and septicemia may be responsible. During the third trimester, ARF may develop from severe PE/eclampsia. Almost 8.9 percent of patients with severe PE can develop ARF, usually associated with HELLP syndrome and abruptio placenta. Other important causes of ARF include uterine hemorrhage with hypotension, prolonged intrauterine fetal death, amniotic fluid embolism and disseminated intravascular coagulation. Multiple factors may operate in the same patient and result in severe ARF. Bilateral renal cortical necrosis occurs more frequently in women with placental abruption. Preexisting nephrosclerosis, renal ischemia, disseminated intravascular coagulation or Schwartzman reaction may predispose to development of renal cortical necrosis.

Bilateral renal cortical necrosis has been observed in 27 to 38 percent of pregnant women with ARF. Some patients with patchy cortical necrosis recover sufficient renal function to survive without dialysis. Since renal biopsies are not done in many cases of ARF, some of these cases go undiagnosed.

ARF Peculiar to Pregnancy

Idiopathic Postpartum ARF

This condition is also known as postpartum malignant nephrosclerosis and postpartum hemolytic uremic syndrome. This follows an apparently normal pregnancy and manifests usually between one day to several weeks after delivery. The onset is a "flu-like" illness followed by rapidly developing renal failure. The BP is usually normal. Congestive cardiac failure and convulsions may occur in some cases. The cause of the syndrome is not clear. Retained placental fragments, oral contraceptives, oxytocin, ergot alkaloids, prostaglandin deficiency and immunologic basis had been postulated as possible causes. Endothelial cell damage is now thought to be the primary abnormality and is associated with unusually large von Willebrand factor multimers which form platelet thrombi in the renal circulation. This resembles a generalized Schwartzman-like reaction. The management is aimed at reducing the BP, if elevated, and supportive measures. The renal function may never recover or do so partially. Although several therapeutic strategies like anticoagulants, antiplatelet drugs, exchange transfusion and antithrombin III supplementation have been tried, there is no convincing evidence that these therapeutic manipulations confer any benefit. Plasma exchange daily or on alternate days for the initial two weeks has been found to be effective, probably by removing the von Willebrand factor multimers. Those who receive kidney transplants do well in the post-transplant period.

ARF in Acute Fatty Liver of Pregnancy

Acute fatty liver of pregnancy is a condition characterized by rapid development of jaundice, normal alkaline phosphatase and microvesicular steatosis usually presenting in the third trimester. More than 50 percent of these patients also develop ARF. The cause of ARF is obscure and may be due to hemodynamic factors as in the hepatorenal syndrome. The mortality is high and often the result of hepatic failure rather than renal failure. Prompt delivery usually improves liver function. Women surviving acute fatty liver of pregnancy have gone through uneventful pregnancies subsequently.

ARF due to Hyperemesis Gravidarum

Persistent vomiting and inadequate fluid replacement may lead to volume contraction and/or hypotension resulting in prerenal failure followed by acute tubular necrosis. This can be prevented by early rehydration and maintenance of intravascular blood volume.

ARF due to Septic Abortion

The pathogenesis of ARF in septic abortion is multifactorial. Bleeding, shock, coagulopathy, septicemia, drugs and nephrotoxic abortifacients are the important pathogenetic factors. In some places, abortifacient paste containing mercury is instilled into the uterus together with a foreign body. Such crude methods result in multiple pathogenetic factors which lead to acute tubular necrosis or renal cortical necrosis.

ARF due to Obstetric Bleeding

Blood loss, hypotension, and volume contraction are the important factors leading to ARF. It may occur in antepartum hemorrhage, placenta previa or postpartum hemorrhage In abruptio-placentae, in addition to the above factors, coagulopathy with disseminated intravascular coagulation may play a very significant role. This may lead to a more severe ARF where the clinical course is more prolonged and recovery of renal function is partial or negligible due to the development of patchy or total renal cortical necrosis. This condition is often suspected if ARF does not recover in 4 to 6 weeks and a renal biopsy provides a definite proof.

ARF from Amniotic Fluid Embolism

Entry of amniotic fluid in the maternal blood may lead to redistribution of body fluids, intravascular volume contraction and hypotension. Protracted hypotension can lead to ARF.

ARF from Obstructive Uropathy

Obstructive uropathy leading to anuria may develop, if the ureter from a single kidney or ectopic kidney is obstructed. Bilateral ureteric obstruction may occur due to tissue trauma and edema of ureter during surgical procedures in the broad ligament. Rarely, accidental ureteric ligation during pelvic surgery may lead to anuric ARF.

ARF from Super-imposed Preeclampsia

The chances of ARF are greater if PE supervenes on a preexisting renal disease.

ARF from Acute Pyelonephritis

While acute pyelonephritis is seldom associated with ARF in the nonpregnant subjects, it is more common is pregnancy, probably due to increased sensitivity of the vasculature to bacterial endotoxin.

Management

The management of ARF per se in pregnant and nonpregnant subjects is essentially similar. However, certain specific conditions which may accompany pregnancy may need attention. In early pregnancy, a retained intrauterine foreign body used for inducing abortion is a consideration particularly if there is infection. Some abortifacients contain nephrotoxic substances like mercury paste, etc. During the third trimester, the extent of concealed hemorrhage may be large and prompt transfusion of adequate quantities of blood is essential. Replacement of fluid or blood must be closely monitored to prevent overcorrection or undercorrection. Since infectious complications may be more common during pregnancy than in the nonpregnant state, the mother should be treated with appropriate antibiotics which are not toxic to the fetus or kidney. Early or prophylactic dialysis is advocated since urea and creatinine cross the placenta and may reduce the chances of fetal survival. If the fetus is viable, termination of pregnancy should be attempted as soon as the maternal condition improves. Since urea and creatinine cross the placenta, the neonate may have higher blood levels of these substances at birth. The osmotic diuresis due to accumulated urea in the neonate must be recognized and managed with prompt rehydration. Both peritoneal and hemodialysis have been advocated in women with ARF in pregnancy. The choice of dialysis therapy has to be individualized. Care is taken to prevent excessive fluid shifts during dialysis. In cases of septic abortion with ARF, aggressive surgical management combined with antibiotic therapy and dialysis support was more useful compared to conservative management combined with dialysis.

URINARY TRACT INFECTIONS IN PREGNANCY

Asymptomatic Bacteriuria

Asymptomatic bacteriuria is characterized by absence of symptoms of urinary tract infection at a time when significant bacteriuria exists. Significant bacteriuria is confirmed when a single suprapubic aspirated sample of urine shows bacterial growth or when two consecutive samples of freshly passed urine yield more than 100,000 colonies per ml of the same organism on culture.

Because of the anatomical and functional changes in the urinary tract and the high urinary nutrients in pregnant women, asymptomatic bacteriuria may occur in 5 to 10 percent of all pregnancies. It is commonly seen in old multiparous women from low socioeconomic background. It is more common when preexisting conditions like diabetes mellitus, sickle cell disease, renal diseases or hypertension are present. Although asymptomatic bacteriuria may be a relatively benign disorder in nonpregnant subjects, 30 to 50 percent of pregnant women with asymptomatic bacteriuria may go on to develop symptomatic urinary tract infection. Asymptomatic bacteriuria may be associated with increased incidence of PE, premature delivery, anemia and low birth weight. Therefore, routine screening of all pregnant mothers during the first trimester for bacteriuria is advocated. If asymptomatic bacteriuria is detected, it is advisable to eradicate the infection with a 14-day course of appropriate antibiotics. Ampicillin, amoxicillin, cephalosporins or kanamycin can be safely used. Short course of ciprofloxacin, nitrofurantoin, nalidixic acid or cotrimoxazole may be used cautiously in pregnancy. These patients should be followed up with serial urine cultures. In women in whom asymptomatic bacteriuria is difficult to eradicate, continuous antibiotic therapy during pregnancy and detailed investigations to rule out urinary tract obstruction in the postpartum period are warranted.

Acute Pyelonephritis

Symptomatic renal parenchymal infection with fever, rigors, chills, loin pain and pyuria may occur in about 1 percent of all pregnancies. Severe infections may lead to sepsis, shock, fetal loss, renal cortical abscess, renal carbuncle and other maternal complications. Asymptomatic bacteriurics, those with previous urinary tract infections or congenital anomalies of the urinary tract, are more prone to develop acute pyelonephritis. A significantly greater pelvicalyceal dilatation has been noted in those developing acute pyelonephritis. The management of acute pyelonephritis in pregnancy should be promptly instituted and performed in the hospital. Urine and blood samples are sent for culture, and treatment with intravenous fluids, antipyretics, and antibiotics are begun. In severe infections, antibiotics which reach high renal parenchymal concentration and have no adverse effects on the fetus should be started immediately. After fever has remitted for several days, antibiotics may be continued by oral route. It may be advisable to give a three-week course of antibiotics to ensure complete eradication of infection. Intermittent urinalysis and cultures are essential to guide control of infection. Tetracyclines are avoided during pregnancy. Co-trimoxazole may cause kernicterus in the neonatal period and hence is avoided near term. In view of ototoxicity, aminoglycosides are preferably avoided. Of the aminoglycosides, kanamycin may be used for severe infection with susceptible organisms. *E. coli* is the commonest organism in more than 70 percent, though Gram positive pathogens can occur later in pregnancy.

PREGNANCY IN PRE-EXISTING RENAL DISEASE

Renal diseases may become manifest during the course of pregnancy or pregnancy may supervene on preexisting renal disease. When proteinuria is first discovered after the twentieth week of pregnancy, an obvious question comes up whether the patient has PE or underlying renal disease, because the clinical features of proteinuria, hypertension, edema and renal insufficiency occur in both settings. The degree of proteinuria does not help in distinguishing between PE and underlying renal disease. Elevated serum uric acid out of proportion to the severity of renal insufficiency is supportive of the diagnosis of PE. Percutaneous renal biopsy may be helpful as glomerular capillary endotheliosis is considered to be specific for PE and almost invariably present, even in mild cases. However, in view of increased vascularity, renal biopsy is usually deferred unless considered essential.

Kidney diseases during pregnancy can affect both the mother and fetus. Hence when a person with preexisting renal disease contemplates pregnancy or conceives, the following questions will be considered:

1. Is conception or continuation of pregnancy advisable?
2. What will be the effect of the renal disease on the pregnancy?
3. Will gestation aggravate renal disease?

Women with moderate or advanced renal failure generally have anovulatory cycles or amenorrhea. If they conceive, it is usually unsuccessful and ends in abortion, intrauterine death or preterm delivery of a severely growth retarded fetus. Women with mild renal failure (serum creatinine < 2.3 mg/dL) may conceive and may be able to go through the pregnancy successfully, if the BP is normal upon conception and maintained at normal level throughout pregnancy. The overall fetal outcome depends on the degree of renal function impairment, degree of control of hypertension and extent of proteinuria on conception. The outlook for the fetus in women who become pregnant despite the presence of renal disease seems favorable as long as significant hypertension is absent and serum creatinine is less than 1.4 mg/dL. The majority of investigations indicate that pregnancy does not influence the natural course of renal disease, if renal function is relatively well preserved and hypertension is absent at conception, though worsening of renal functions are common in moderate to severe renal failure. It was reported that in lupus nephritis, IgA nephropathy, membranous glomerulopathy or focal and segmental glomerulosclerosis further deterioration of the original disease may occur. However, it now appears that risk factors like nephrotic range proteinuria, hypertension and impaired renal function have a more important role. If the serum creatinine is more than 1.5 mg/dL, pregnancy can accelerate renal damage and if it exceeds 2 mg/dL, more than one third can worsen their renal functions. Renal disease complicated by pregnancy must hence be considered "high risk" pregnancy and must be managed with close fetal and maternal monitoring by an experienced team of nephrologists and obstetricians. They will require more frequent visits and monthly renal function test. It is generally recommended that the BP should be kept below 140/90 mm Hg.

Acute Glomerulonephritis

Women who conceive during the resolving phase of acute glomerulonephritis may not need any aggressive management. Those who develop acute nephritis in pregnancy also may be managed as in nonpregnant state.

Chronic Glomerulonephritis

Although superimposed PE and hypertensive complications may occur more frequently in women with chronic glomerulonephritis, pregnancy may be successful if hypertension is adequately controlled and renal function is normal.

Polycystic Kidneys

When one of the spouses has autosomal dominant polycystic kidney disease, the couple should undergo counseling. The high chances of transmitting the disease to the offspring and its implications are explained to them and the decision to conceive is left to them. Women with asymptomatic polycystic kidneys usually have an uneventful pregnancy. If the enlargement of the kidneys is massive, it may cause mechanical hindrance for the enlargement of the uterus during the later stages of pregnancy.

Nephrotic Syndrome

Woman with proteinuria less than nephrotic range may develop increased proteinuria in the nephrotic range during pregnancy due to increased GFR, changes in the filtration mechanism or a rise in venous pressure. Women with nephrotic syndrome but in remission may relapse during pregnancy. Nephrotic syndrome is managed by appropriate fluid restriction. Normal salt intake is permitted but diuretics are avoided. Although a protein-restricted diet has been advised in nonpregnant subjects with nephrotic syndrome, this is not followed during pregnancy. The fetal development may be affected and small for date babies are common, if fetal development takes in the unfavorable environment of hypoalbuminemia. Regular albumin infusions are advocated until delivery. Specific treatment with corticosteroids can be given if indicated, whereas other immunosuppressive drugs are usually commenced after delivery.

Diabetic Nephropathy

The problem of diabetic nephropathy and pregnancy is particularly relevant in juvenile diabetics. If the diabetes has been present for many years at the time of conception, microscopic changes may have developed in the kidneys. These women have greater chances of developing bacteriuria or PE. Although proteinuria may become severe during pregnancy, it returns to the prepregnant levels after delivery and the gestation does not seem to alter the course of maternal diabetic nephropathy.

Systemic Lupus Erythematosis

The effect of gestation on lupus and the effect of lupus on gestation are variable. If the woman has no lupus activity for at least one year before conception and renal function is normal, she has a good chance of an uneventful pregnancy with no apparent aggravation of lupus activity postpartum. If the woman had active lupus at the time of conception or the symptoms develop during pregnancy for the first time, the outcome may be unfavorable. Flares can occur during pregnancy, especially in those having thrombocytopenia and hypertension, but are usually mild to moderate. In about 10 percent of patients, there may be an exacerbation of lupus activity postpartum leading to ARF. For this reason, some centers still increase the dose of steroids prophylactically after delivery and reduce it over the next three months. The autoantibodies may cross the placenta and result in repeated abortions. Such patients may need drug therapy for control and may be able to go through a successful pregnancy while on low-dose steroid therapy. The presence of antinuclear antibodies may be responsible for the lupus syndrome in the neonate characterized by transient skin rash, pancytopenia or heart block. Lupus nephritis class III to IV is a risk factor for hypertensive disease during pregnancy, but it does not contraindicate gestation. Pregnancy is safe for the majority of mothers if it is planned when SLE is quiescent. Although fetal risk has been progressively reduced in the last 40 years, it continues to be higher than that occurring in pregnancies of healthy women. In particular, the presence of antiphospholipid antibodies considerably worsen the fetal outcome. Some feel that the deterioration of renal function seen in some pregnant lupus patients may not be influenced by pregnancy and could be the natural course.

Vascular Disorders

Polyarteritis nodosa, scleroderma and Wegener's granulomatosis are associated with hypertension and significant vascular involvement. Hence the outcome of pregnancy is uniformly poor. Even maternal deaths have been reported and such patients should be advised against pregnancy.

Chronic Tubulointerstitial Nephritis, Reflux Nephropathy and Urolithiasis

In all these conditions, the chances of developing symptomatic urinary tract infections are high. Such women are monitored closely by frequent urine cultures and suitable antibiotics used at the appropriate time. If the BP and renal functions are in the acceptable range, the outcome of pregnancy is favorable. Prophylactic ureterovesical reimplantation in women with repeated pyelonephritic episodes may be advisable in women with persistent vesicoureteric reflux contemplating pregnancy. In urolithiasis, adequate hydration is maintained and analgesics used, if necessary.

PREGNANCY AND DIALYSIS

To optimize pregnancy outcome in the pregnant lady with renal failure, it is recommended to initiate hemodialysis when the serum creatinine exceeds 5 mg/dL or the BUN exceeds 60 mg/dL with the goal being a predialysis BUN below 50 mg/dL with normalization of systemic pH, calcium, phosphorus and potassium. Five to seven hemodialysis sessions per week may be required with bicarbonate buffer. Intensive nocturnal hemodialysis may give a better outcome. Fluid balance should be maintained and abrupt fluid shifts during dialysis avoided. The BP should be closely monitored and hypotension avoided. Anticoagulation should be very carefully planned to avoid hemorrhagic complications. In women who develop ARF during pregnancy, early dialysis is advocated and continued till renal function recovers or improves. Both hemodialysis and peritoneal dialysis can be used. Women on maintenance hemodialysis may conceive. Nearly 50 percent may abort spontaneously. In view of the risks and overall poor outcome, most women prefer therapeutic abortion. However, there are reports of successful pregnancy in women who have been on maintenance hemodialysis for months or years. Successful pregnancies have also been reported in diabetic women on continuous ambulatory peritoneal dialysis.

PREGNANCY FOLLOWING RENAL TRANSPLANTATION

Renal transplantation is the best treatment for fertile women with end-stage renal disease who want to become pregnant. Women who are keen to conceive after successful transplantation may be advised to do so only around two years after transplantation provided renal function and BP are normal and there is no significant proteinuria. The patient should be monitored closely by a team of nephrologists and obstetricians in a high risk pregnancy unit. Although the graft functions are rarely affected, there is an increased risk of spontaneous abortions, premature deliveries, low birth weight, PE and cesarean sections. The incidence of fetal malformations due to immunosuppressive drugs does not seem to be a significant problem with prednisolone, azathioprine or cyclosporine, though there is little experience with the newer drugs. However, the urinary protein excretion and

BP tend to increase as pregnancy advances. Meticulous sterile precautions are undertaken during various procedures as the chances of infection are greater in these immunosuppressed women.

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Renovascular Disease

Ricardo Paz-Fumagalli

INTRODUCTION

Reduced arterial flow to the kidney causes renovascular hypertension and ischemic nephropathy. While renal artery stenosis (RAS) can cause severe hypertension and renal function loss, and treatment has been shown conclusively to reverse the pathophysiologic cascade that leads to blood pressure and functional abnormalities, opinions and attitudes toward interventional management can vary from one specialty to another. The frequency of endovascular intervention with stenting to treat atherosclerotic RAS is rising, increasing from 7,760 Medicare claims for this procedure in 1996, to 18,520 in 2000, and an estimated 350,000 claims in 2005. This increase has been particularly pronounced among cardiologists. The nephrology community has a considerably more cautious approach because the clinical trials so far have been largely incapable of demonstrating benefit after revascularization.

The investigation of renovascular disease is facilitated by major improvements in imaging techniques, and is easier and safer than ever to treat with the availability of angioplasty and stenting. Moreover, there is an important role for bypass surgery, as decades of experience point at durable clinical benefit and can be done very safely in appropriately selected patients. The benefits of renal revascularization are improvement or elimination of hypertension, stabilization or improvement of renal function, and improvement of certain unstable cardiac conditions such as congestive failure, often referred to as "flash pulmonary edema". Procedural complications and negative results of clinical trials have dampened the enthusiasm for angioplasty, stenting and surgery. Yet, most practitioners in nephrology, vascular surgery, cardiology, and interventional radiology have seen excellent results from revascularization in many patients.

PATHOPHYSIOLOGY

Renovascular hypertension results from decreased blood flow into the kidney, usually caused by stenosis or occlusion of the renal artery. The causes for renovascular hypertension are multiple, most commonly atherosclerosis and fibromuscular dysplasia (FMD) (Table 1).

In the 1930s Goldblatt conducted experimental studies that demonstrated that reduced perfusion of the kidney can increase the systemic blood pressure. Renovascular hypertension involves the activation of

Table 1. Causes of renovascular hypertension

Atherosclerosis
Fibromuscular dysplasia
Extrinsic compression
Aortic or renal artery dissection
Embolization
Renal compression (Page kidney)
Arteritis Takayasu Polyarteritis nodosa
Radiation
Infarction
Neurofibromatosis

the renin-angiotensin-aldosterone system and varies pathophysiologically depending on the pattern of disease. The experimental models of 2-kidney-1-clip and 1-kidney-1-clip are equivalent to human cases of unilateral RAS in the presence of a normal contralateral kidney (2-kidney-1-clip) and bilateral RAS or RAS in a solitary kidney (1-kidney-1-clip).

The two disease patterns are different physiologically, as either angiotensin II or volume mechanisms will largely determine the development of hypertension. In the 2-kidney-1-clip model the hypertension is maintained by angiotensin II and blood tests will show elevated plasma renin activity. The normal kidney responds with natriuresis, which will tend to lower the blood pressure, but the patient will remain hypertensive. In the 1-kidney-1-clip model (bilateral RAS or solitary kidney with RAS) the individual does not possess a normal kidney to respond with natriuresis, consequently the hypertension has a more direct relationship with salt and water retention, and plasma renin activity tends to remain normal. The hypertension therefore is volume dependent. The variability in the renin activity in patients with occlusive renal artery disease is an important reason why selective renal vein sampling for renin measurement has limited clinical usefulness.

Hypertension in occlusive renal disease is complex and involves mechanisms beyond the renin-angiotensin-aldosterone system. Oxidative stress, endothelium derived endothelin, sympathetic activity, and prostaglandins have a role in long-term renovascular hypertension, when influences from the renin-angiotensin-aldosterone system gradually decrease and are no longer predominant. Sympathetic activity can lead to sodium resorption and volume expansion, and can activate the renin-angiotensin-aldosterone system.

Progressive arterial narrowing will change flow little until a critical point is reached and the flow starts decreasing rapidly with increasing obstruction. This critical narrowing corresponds in experimental models to luminal *cross-sectional area* reduction of 75 percent or more, or 50 percent or more luminal *diameter* reduction. Diagnostic methods and management are based on estimation of the degree of luminal narrowing. Traditionally, a lesion is considered significant when the luminal diameter reduction is 50 percent or greater. However, many patients with this degree of RAS do not have evidence for renovascular disease, and when symptoms are present the response to therapy varies widely. It appears that angiographic diameter reduction greater than 70 percent, or development of a pressure gradient across the stenosis of at least 10 to 20 mmHg, is necessary for increased secretion of renin.

The impairment in renal function caused by RAS or occlusion has been termed ischemic nephropathy, but probably is not truly ischemic, since blood oxygen level-dependent magnetic resonance values show that kidney oxygenation is preserved in patients with RAS. However, we know that atherosclerotic RAS can worsen over time and can progress to occlusion, as observed in 16 percent of medical therapy group patients in the DRASTIC clinical trial. There is a strong correlation between occlusion of the renal artery and kidney atrophy, and occlusive disease is responsible for a substantial minority of patients requiring dialysis. The progressive nature of atherosclerosis is a threat to kidney function, but the relationship between RAS and renal dysfunction is complex. RAS can cause a decrease in glomerular filtration rate, but this is not the case in unilateral disease, and GFR alone does not explain the azotemia in most cases. Evidence is emerging that kidney deterioration is at least in part the result of the interaction between abnormal renal perfusion and the atherogenic process leading to kidney fibrosis. Renal dysfunction in patients with atherosclerotic disease does not exactly correlate with the degree of renal artery narrowing and renal dysfunction in patients with atherosclerotic disease can occur independent of renal artery narrowing. Additionally, the degree of RAS does not correlate closely with response to angioplasty or stenting. The observation that even severe bilateral FMD may not lead to renal insufficiency suggests that mechanisms other than simple reduction in blood flow are behind the loss of kidney function in atherosclerosis.

RAS has been associated with unstable cardiac syndromes, including flash pulmonary edema and acute coronary syndrome, in which sodium retention and increased volume are of great significance. Renin production and increased angiotensin and aldosterone can be reversed by renal artery revascularization and the patient's sodium homeostasis can be restored. Many patients with RAS tolerate the use of angiotensin antagonists but others can develop acute renal insufficiency, particularly in the presence of bilateral RAS.

EPIDEMIOLOGY

The great majority of RAS is atherosclerotic but FMD is responsible for an important minority of cases. Atherosclerosis is most common in patients over the age of 50 and symptomatic FMD is most prevalent in young women. The prevalence of RAS parallels the progression of atherosclerosis. RAS had a high prevalence in patients with peripheral vascular disease (25.3 percent), abdominal aortic aneurysm (33.1 percent), end-stage renal failure (40.8 percent), and heart failure (54.1 percent). Among high risk groups there is a high prevalence of RAS, but hypertension is not universal. Renovascular hypertension therefore occurs only in a portion of cases of RAS. Essential hypertension is much more common than renovascular hypertension, but the latter should be suspected when certain clinical characteristics are observed (Table 2). FMD can be asymptomatic and has been reported in 3 percent of potential renal donors.

DIAGNOSTIC TESTING

The diagnostic approach to RAS generally is two tiered. A number of noninvasive tests are available for screening, and invasive tests are applied for confirmation and when the intention is to treat. The first step is to identify the population at risk, to which the screening process is applied. Table 2 offers clinical clues that should prompt the clinician to apply diagnostic testing.

Screening tests have weaknesses and strengths that reflect anatomic and physiologic features of renovascular disease. The most common site of RAS is the arterial ostium, but the important group of FMD characteristically does not have ostial disease.

Computed tomography angiography (CTA) and magnetic resonance angiography (MRA) are ideally suited to evaluate the renal ostium, usually are strictly anatomic studies, and are less accurate with the reduction in size and greater inherent motion of more distal arterial segments. Both CTA and MRA require intravenous injection of contrast agents. Care is needed to avoid patients at risk for iodinated contrast nephropathy or gadolinium-related nephrogenic systemic fibrosis (NSF), and those with contrast allergy. Doppler ultrasound is completely safe and noninvasive, provides a more physiologic evaluation with greater emphasis on the distal renal vasculature, is capable of ostial examination, but has limitations when the arteries are poorly visualized or multiple and small. Radionuclide renography with angiotensin-converting-enzyme inhibitor captopril has low sensitivity and specificity, likely as a result of the variability in renin levels in cases of renovascular hypertension, the confounding influence of other types of hypertension, frequent presence of renal insufficiency and the possibility of symmetric bilateral RAS. When patients are appropriate candidates for treatment, invasive diagnostic tests are indicated. Although conventional catheter-based angiography is considered the gold standard, there are technical and physiologic limitations that decrease the diagnostic accuracy, and even when unequivocally significant, reversal of the RAS may not have the desired clinical benefit.

Duplex ultrasonography, CTA (in individuals with normal renal function) and MRA can be used to establish the diagnosis of RAS. Conventional angiography is recommended when the clinical index of suspicion is

Table 2. Indications for performance of diagnostic studies for renal artery stenosis

Hypertension before the age of 30 years or severe hypertension after the age of 55 years.
Accelerated hypertension (sudden and persistent worsening of previously controlled hypertension).
Resistant hypertension despite full doses of an appropriate 3-drug regimen that includes a diuretic.
Malignant hypertension (evidence of acute end-organ damage; i.e., acute renal failure, acutely decompensated congestive heart failure, new visual or neurological disturbance, and/or advanced retinopathy).
New azotemia or worsening renal function after the administration of an ACE inhibitor or an angiotensin receptor blocking agent.
Unexplained atrophic kidney or a discrepancy in size between the 2 kidneys of greater than 1.5 cm.
Sudden, unexplained pulmonary edema, especially in azotemic patients ("flash" pulmonary edema).
Unexplained renal failure, including individuals starting renal replacement therapy (dialysis or renal transplantation).
Aortography or renal angiography may be indicated at the time of coronary arteriography in patients with multivessel coronary artery disease.
Unexplained congestive heart failure or refractory angina.
Source: Hirsch AT, et al. ACC/AHA Task Force on Practice Guidelines, 2005.

high and the results of noninvasive tests are inconclusive. Captopril renal scintigraphy, selective renal vein renin measurements, plasma renin activity and the captopril test (measurement of plasma renin activity after captopril administration) are weak screening tests. Selective renal vein renin sampling is particularly unreliable in bilateral disease and may have its greatest usefulness in identifying patients with renal artery occlusion that may benefit from nephrectomy. The captopril renin activity test is unreliable with expanded volume, renal insufficiency, bilateral RAS, or a solitary kidney.

Doppler Ultrasound

Doppler ultrasound is the most cost-effective and safest diagnostic method for RAS. It can identify hemodynamically significant lesions and provide the kidney length, quality of the cortical thickness, and the presence of parenchymal lesions or urinary tract stones. It is accurate in the presence of a renal artery stent. Doppler ultrasound is most useful when positive for hemodynamic abnormalities. Negative studies are less reliable because the test is very operator dependent and limited by intestinal gas, obesity and multiplicity of renal arteries. Diagnostic criteria strive to identify lesions that correspond to angiographic narrowing ≥70 percent to select patients most likely to benefit from treatment.

The sonographic exam with an anterior approach allows direct color Doppler examination of the renal artery trunks and aorta near the renal ostia. The insonation angle should be corrected to <60 degrees. Analysis of spectral waveforms determines values of peak systolic velocity in the aorta and renal arteries and end-diastolic velocities of renal arteries. The renal/aortic peak systolic velocity ratio is calculated. The operator observes for flow jets and turbulence. Ideally the patient should be fasting because this portion of the exam is quite vulnerable to intestinal gas and obesity.

Next, indirect evidence of the condition of the renal artery is obtained from a posterolateral transrenal approach, with examination of intrarenal segmental arterial waveforms. This part of the exam can be successfully completed in most subjects, emphasizes hemodynamics, but produces only limited vascular anatomic information. The spectral waveforms are examined for the characteristics of the signal upstroke, flow acceleration and presence of early systolic peaks. The resistive index and acceleration time are calculated. Angle correction is not needed for *segmental* arterial waveform analysis. It is recommended that at least three values of resistive index from different parts of the kidney be averaged. Cardiac arrhythmias can make measurements of resistive index unreliable.

The Doppler ultrasound diagnosis of RAS is based on demonstration of high velocities in the main renal artery trunk and poststenotic Doppler changes. A renal artery trunk peak systolic velocity >200 cm/sec correlates with 60 percent angiographic RAS. End-diastolic velocity >150 cm/sec correlates with 80 to 99 percent angiographic RAS (unreliable if resistive index >0.7). The renal/aortic peak systolic velocity ratio helps to compensate for differences in cardiac output, and renal/aortic peak systolic velocity ratio >3.5 correlates with 70 percent angiographic RAS. This value is not reliable if there is an abdominal aortic aneurysm, the aortic peak systolic velocity is <40 cm/sec, or the side-to-side resistive index difference is ≥0.05.

A resistive index >0.8 can predict failure of RAS revascularization, probably because the increased peripheral resistance is a reflection of parenchymal renal disease, and even if RAS is absent, resistive index >0.8 predicts a decline in renal function, need for dialysis and death. In cases of unilateral RAS a resistive index difference between the kidneys >0.05 correlates with a significant RAS, and if <0.05 serial follow up is recommended to detect progression. For bilateral RAS the resistive index difference is not reliable. Poststenotic dampening of the systolic upstroke will alter the acceleration time and produce the tardus-parvus (dampened) waveform pattern. An acceleration time >0.07 seconds is abnormal and implies a significant RAS. As is the case with resistive index, changes in acceleration time can be used to follow progression of disease.

Computed Tomography Angiography

Multidetector computed tomography technology combined with thin collimation and timed intravenous contrast bolus with high injection rate can produce angiographic images. The axial acquisitions are routinely subjected to postprocessing of the raw data. The data manipulation techniques that are most useful include multiplanar (i.e., coronal and sagittal) reformatting with maximum-intensity-projection (MIP), three-dimensional (3-D) reconstructions with MIP and with shaded-surface rendering, and volumetric manipulations on a computer workstation. Breath-hold techniques and fast scanning eliminate much of the spatial resolution loss caused by motion, including pulsations and respiration.

CTA details plaque, but calcified plaque can reduce the usefulness of shaded-surface 3-D reconstructions and can interfere with estimation of luminal narrowing (Figs 1A and B). The 3-D reconstructions can be very helpful when facing confusing tortuosity and vascular overlap. CTA can show small accessory renal arteries. Drawbacks of CTA are exposure to iodinated intravenous contrast in patients with a decline in renal function, its inability to clearly show the arterial lumen after stent placement, and the exposure to ionizing radiation. CTA is not contraindicated in cases of mild renal insufficiency and precautions such as intravenous hydration and use of isoosmolar contrast can be observed. Suggested modifications to contrast use depending on renal function are presented in Table 3.

CTA is most accurate proximally, with loss of detail in the distal main artery and hilar branches. For this reason, CTA is best for atherosclerosis and less accurate for FMD.

Magnetic Resonance Angiography

MRA is highly reliable in detailing the renal artery trunks, can accurately identify multiple renal arteries, and provides information on kidney size, anatomic quality of the renal cortex and incidental pathologies. MRA is not substantially affected by heavily calcified plaque, does not expose the patient to contrast-nephropathy or ionizing radiation, and intravenous contrast can be used in patients with some degree of renal insufficiency. MRA is still inferior to conventional catheter angiography in demonstration of atherosclerotic branch stenoses or FMD.

Table 3. Intravenous iodinated contrast media for renal artery computed tomography angiography: utilization guidelines based on renal function

eGFR (ml/min)	*Contrast medium**	*Volume*
≥60	Iohexol 300 mg I/mL	100 ml
45-60	Iodixanol	100 ml
30-44	Iodixanol	Lowest possible dose plus intravenous hydration
<30	Avoid	

eGFR = estimated glomerular filtration rate; I = iodine

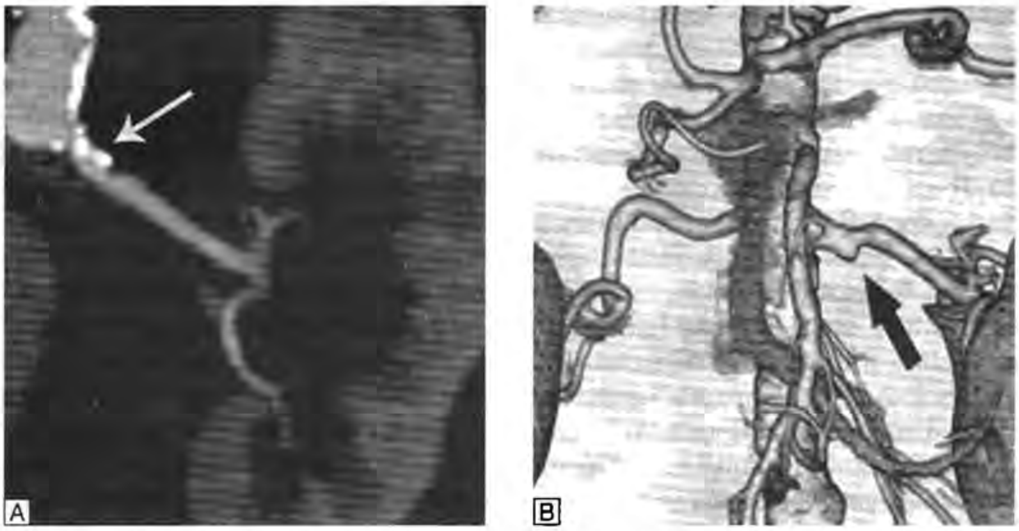
*Institutional choice according to patient population and product availability. The author's practice has adopted universal use of nonionic contrast for intravenous use.

MRA diagnosis is facilitated by multiplanar, volumetric and 3-D displays. Although MRA can examine the renal arteries without intravenous contrast agents, typically with time-of-flight or phase-contrast techniques, the enhanced MRA provides the greatest vascular detail. 2-D or 3-D time-of-flight acquisitions in the coronal plane are most commonly used (Fig. 2). Similarly to CTA, manipulation of data with creation of multiplanar and 3-D reconstructions and volumetric examination on a computer workstation help clarify the degrees of stenosis and unravel tortuous and overlapping arteries. MRA is vulnerable to artifacts, motion, and is contraindicated in patients with pacemakers, some cerebral aneurysm clips, certain types of implants (ear, valvular) and patients with ferromagnetic foreign bodies in delicate locations such as the orbits. Though usually not stated by the manufacturers, renal artery stents generally are safe in the MRI magnet bore.

An important risk of MRA is NSF. This is a condition of patients with chronic renal insufficiency characterized by thickening, edema, induration and discoloration of the skin. The disease can be progressive, have multiorgan involvement, and can be fatal. NSF has been linked to the use of gadolinium in patients with renal insufficiency. Depending on the chemical composition of the contrast agent the risk will vary, and is greatest with gadodiamide. Gadobenate dimeglumine does not appear to have the same association. The estimated glomerular filtration rate (eGFR) offers a practical approach to use of contrast. In patients with eGFR >60 ml/min/1.73 m^2 any contrast agent commercially available can be used. If the eGFR is 30 to 60 ml/min/1.73 m^2 gadobenate dimeglumine in full or reduced dose is recommended, and for eGFR <30 ml/min/1.73 m^2 the options are to perform the exam without contrast, choose an alternative imaging modality, or use gadebenate dimeglumine with a reduced dose. Gadolinium is usually avoided completely in patients receiving dialysis.

Conventional Catheter Angiography

The standard for diagnosis of RAS is intra-arterial digital subtraction angiography (DSA) often done with pressure gradient measurements. DSA is used for diagnostic purposes in a small portion of cases because most can be evaluated with noninvasive methods. It remains critical in the management of RAS in patients that fall into the clinical categories listed in Table 2 in whom noninvasive testing was nondiagnostic.



Figures 1A and B: Computed tomography angiogram data processed into curved maximum intensity projection 2-D reconstruction (A) of the left renal artery showed heavily calcified ostial plaque causing a severe stenosis (white arrow). Notice the severe narrowing of the contrast-enhanced lumen. Three-dimensional reconstruction using a surface-rendered technique (B) failed to demonstrate the stenosis. The heavily calcified plaque as displayed is indistinguishable from the contrast-enhanced arterial lumen (black arrow). This example illustrates the limitations of data manipulation techniques. Three-dimensional reconstructions are best interpreted in conjunction with the axial source images

A significant gradient across the RAS indicates hemodynamic importance and is a criterion commonly used to indicate revascularization. In general, a pressure gradient across a stenosis is significant when >10 mmHg or about 10 percent or more of the systolic pressure. The most common methods for gradient calculation are to advance a catheter across the stenosis and do simultaneous renal and aortic pressure measurement using a sheath and the selective catheter, or to do a "pull-back" measurement with a single diagnostic catheter. In small arteries or tight stenoses these methods can overestimate the gradient by contributing to the obstruction with the catheter itself. The ideal gradient measurement tool is a pressure measuring wire because the small caliber does not significantly add to the arterial narrowing. In most practices the gradient measurement is catheter based. Many patients with stenosis of 50 to 70 percent do not respond to resvascularization. For this reason a narrowing >70 percent has been proposed as a criterion to indicate therapy and to better select patients that will benefit from treatment. The value of pressure gradient measurement has been questioned by investigators that could not find a correlation

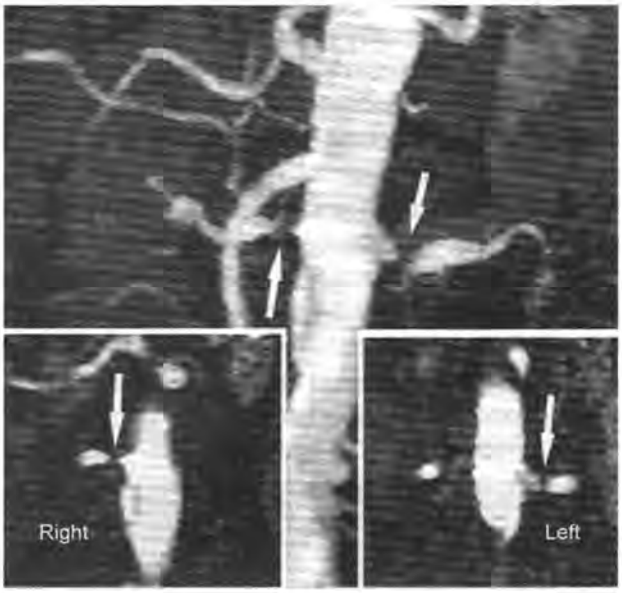


Figure 2: Abdominal aortic magnetic resonance angiogram obtained with intravenous gadolinium in a 70-year old female with several years of severe hypertension (200/80 mmHg) and stage III chronic kidney disease with creatinine of 1.6 mg/dL. Maximum intensity projection 3-D reconstruction shows severe bilateral atherosclerotic ostial renal artery stenoses (arrows)

between the blood pressure response to renal artery stenting and translesional pressure gradient values, but luminal narrowing and pressure gradient measurements remain the most commonly applied invasive criteria to determine significance.

Newer technology provides images of diagnostic quality with dilute iodinated contrast and with CO_2 gas, which are particularly useful maneuvers in patients at risk for nephrotoxicity. The main disadvantages of DSA are the risks of radiation exposure, contrast-related nephrotoxicity or allergy, and arterial injury resulting in hemorrhage, thrombosis or dissection. Many patients receive procedural intravenous hypnotics and narcotics, introducing risks inherent to sedation. DSA is also the most expensive diagnostic method and requires a substantial time commitment on the part of medical personnel and patients alike.

Comparison of MRA, CTA and DSA

CTA and MRA have sensitivities of 94 to 100 percent and specificities of 92 to 99 percent, and are superior to ultrasonography, captopril scintigraphy and the captopril test, using DSA as the diagnostic standard. However, the RADISH prospective multicenter comparative study of the diagnostic accuracy of CTA and MRA yielded a lower sensitivity and specificity of 64 percent and 92 percent for CTA, and 62 percent and 84 percent for MRA. The findings for RAS caused by FMD were dismal, with sensitivity of 22 percent and 26 percent for MRA and CTA. This study concluded that DSA should remain the diagnostic method of choice because CTA and MRA did not prove to be reproducible or sensitive enough to rule out RAS.

These data were contrary to previous reports and the experience of practicing radiologists. There are number of possible explanations for the poor performance of CTA and MRA in the RADISH trial. The technology in 1998 to 2001 was considerably less capable than today, image postprocessing methods have been refined, and interactive computer workstations are now widely available. Other factors include better performance with ostial lesions compared to nonostial, the high proportion of FMD in the study, the imperfection of DSA as a reference standard, and the blinded nature of the study interpretations. This controversy is not resolved, but most radiologists find CTA and MRA to be highly accurate. More recent studies, albeit small, have again shown sensitivities and specificities approaching 100 percent and suggest that MRA and CTA can replace DSA as an initial diagnostic test for RAS. We can conclude that CTA and MRA are accurate methods, but DSA remains the standard and should be done when the need to establish the diagnosis of RAS is essential.

Novel Diagnostic Methods

Because many patients with RAS do not benefit from revascularization, diagnostic tests capable of predicting response are much needed. The reference standard, DSA and pressure gradient measurement, is not reliably predictive of blood pressure improvement after invasive treatment. Two methods have been found that correlate with response to therapy. Renal fractional flow reserve (FFR) is based on the principle that blood flow across a stenosis will be maximal when the peripheral resistance is minimized. FFR is calculated after intra-arterial administration of papaverine for vasodilatation. Patients with normal FFR tend to be nonresponders and those with abnormal FFR have a high likelihood of blood pressure improvement. The greatest disadvantage of FFR is that it requires diagnostic catheterization. The second method is measurement of brain natriuretic peptide (BNP) levels. High levels have correlated with hypertension improvement. If other investigators confirm the predictive value for response to therapy that FFR and BNP seem to provide these tests would be a welcome addition to the diagnostic arsenal, especially BNP because it is noninvasive.

MANAGEMENT OF RENOVASCULAR DISEASE

Management of renovascular atherosclerotic disease is complex. Many therapeutic objectives are shared with other manifestations of atherosclerosis such as a coronary, cerebrovascular and peripheral artery disease. Treatment has the intent of reducing cardiovascular mortality, prevent cardiac and cerebrovascular events, and stabilize renal function. Control of hypertension and diabetes, treatment of hypercholesterolemia, cessation of smoking, and weight loss apply to all patients before and after interventions for RAS.

Antihypertensive Drug Therapy

Antihypertensive treatment is beyond the scope of this chapter, but some basic principles can be outlined. In most patients with RAS complete reversal of hypertension occurs only in a minority and drug therapy for hypertension is necessary before and after revascularization. Because there is no conclusive proof that revascularization offers any advantage in patient's that have well controlled hypertension with medication alone, those with easily managed hypertension do not require a diagnostic workup for RAS. When the response to therapy is unsatisfactory, intervention for RAS gains importance.

The severity of hypertension and the likelihood of target organ injury (left ventricular hypertrophy, congestive heart failure, proteinuric kidney disease) are greater for renovascular than for essential hypertension. Although counteracting the renin-angiotensin-aldosterone system activated by renal arterial obstruction and the use of diuretics are thought to be critical in most patients, some authors argue that angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blocking (ARB) agents may be important contributors to renal deterioration and need for dialysis. Drug therapy can be complicated by induction of azotemia in patients with RAS as angiotensin blockade reduces filtration by blocking the increased efferent arteriolar tone needed to maintain function distal to the stenosis. Azotemia is most commonly seen in cases of bilateral RAS or RAS in a solitary kidney, elderly patients, in those that are volume depleted, and in cases of pre-existing renal insufficiency.

The benefit of lipid control cannot be underestimated. In experimental models the combination of RAS and hypercholesterolemia causes damage greater than that of hypertension alone. GFR is significantly reduced and tissue inflammation and fibrosis are accelerated. A number of mechanisms that involve inflammatory and growth factors, and production of oxidative agents contribute to cause harm of the kidney tissue distal to the stenosis. Control of hypercholesterolemia with simvastatin slows the development of renal fibrosis, potentially preserving kidney function.

Renal Artery Revascularization

For several decades renal artery revascularization has provided clinical improvement in selected patients. However, the results of revascularization often fall short of expectations. This also holds true for attempts at stabilization or restoration of renal function associated with atherosclerotic disease of the renal artery ostium. Although our understanding of the reasons for a poor response have become clearer, it is still difficult to identify patients that will see clinical benefit from improved arterial flow. To complicate matters, the morbidity and potential mortality of endovascular and surgical repair of RAS sometimes will negate the benefit of treatment. Yet, nephrologists, vascular surgeons, cardiologists and interventional radiologists have observed and documented excellent results of revascularization in many patients (Figs 3A and B). This chapter emphasizes endovascular techniques, as discussion of surgery is beyond its scope, and because endovascular techniques by 2004 were responsible for over 98 percent of renal artery revascularizations in the United States.

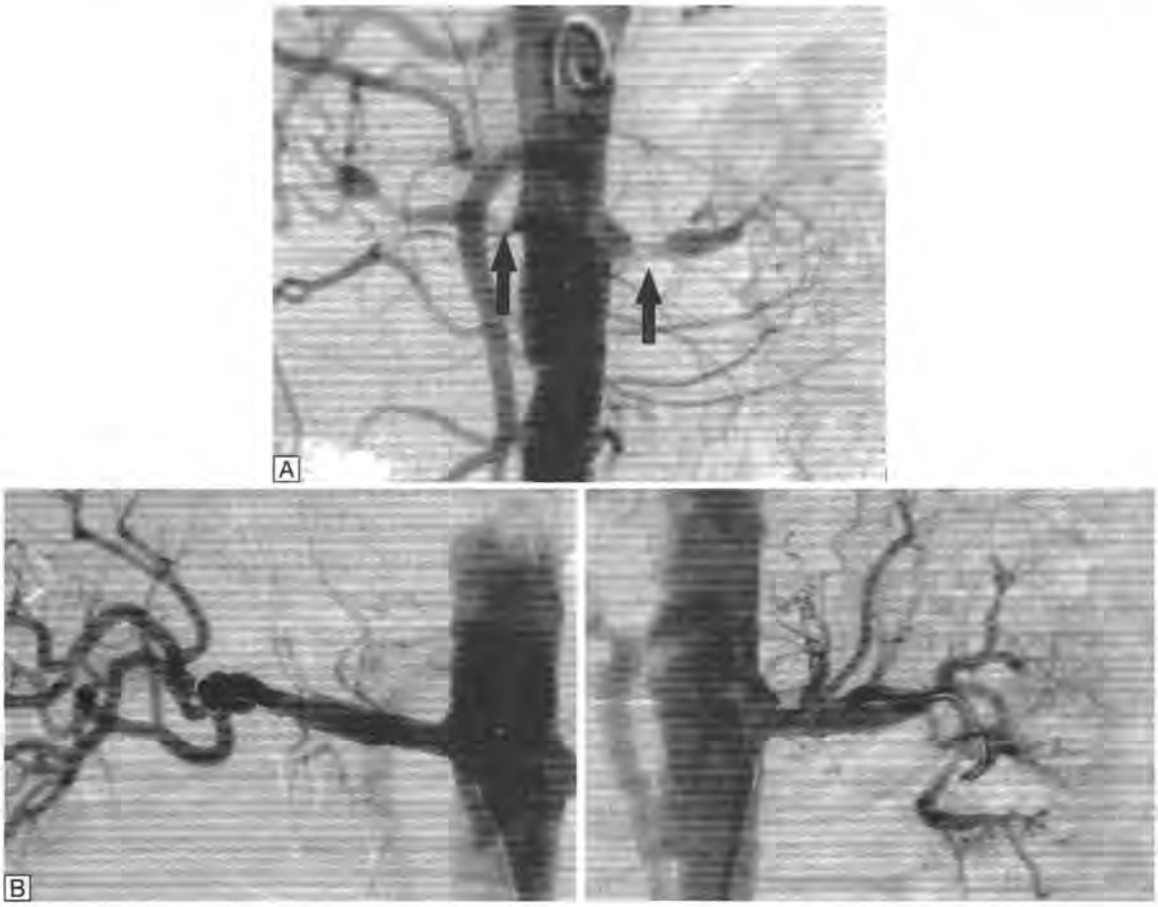
Patient Selection

Patient selection for renal artery revascularization is the final step in a process that starts with a high level of suspicion. In broad terms, the patient population that should be investigated for RAS presents with hypertension difficult to control, progressive renal failure, and cardiac instability with recurrent pulmonary edema and refractory congestive cardiac failure. Table 2 summarizes the indications for diagnostic testing for RAS.

Revascularization is favored if there is progressive decline in GFR during treatment of systemic hypertension, failed medical therapy for hypertension, GFR deterioration while on ACE inhibitors or ARBs, or recurrent congestive heart failure in a patient in whom the adequacy of left ventricular function does not explain the degree of failure. Imaging and laboratory findings are also useful in excluding certain individuals from revascularization. Doppler ultrasound resistive index ≥0.8, proteinuria >1 g/day and creatinine clearance <40 ml/min predict poor response to angioplasty and increased risk for renal failure and death.

Balloon Angioplasty and Stenting: General Considerations

A discussion of the pre-, intra-, and postprocedural aspects of angioplasty is beyond the scope of this chapter. Complications are an important reason why only properly selected patients should be offered intervention. The most common and important risks



Figures 3A and B: Conventional abdominal aortogram (A) of the patient presented in Figure 2 confirmed the bilateral renal artery stenoses. Composite image of bilateral selective renal angiograms (B) after revascularization with balloon-expandable metallic stents showed normalization of the ostial arterial lumen diameter. The baseline creatinine of 1.6 mg/dL gradually improved and 30 months later it was stable at 1.2 mg/dL

are contrast reactions and nephrotoxicity, puncture-related hemorrhage or pseudoaneurysms, arterial trauma causing hemorrhage, intimal dissection or acute arterial occlusion, atheroembolism, worsening renal function possibly leading to dialysis, and rarely death. Although restenosis after angioplasty or within stents is a recurrence of arterial obstruction rather than a procedural complication, it represents an important problem that requires attention.

Atheroembolization

Cholesterol embolization is a disease with systemic manifestations, as emboli originating from the aorta can lodge anywhere in the body. The kidneys are vulnerable to this process, particularly during revascularization for RAS, and can originate from the aortic wall or plaque in the renal artery. Renal atheroembolization can present acutely, subacutely, or with a chronic pattern. The pattern typically seen in renal revascularization is subacute, developing over weeks or months, and the functional deterioration usually occurs gradually. The cholesterol crystals act as intravascular foreign bodies, cause intense inflammation, and the end result is progressive fibrous endarteritis that causes vascular occlusion (Fig. 4). The diagnosis can be facilitated by typical findings in skin and other organs when the origin of emboli is the aorta, but these clues are not helpful when emboli happen during vascular intervention of the renal vasculature. Diagnosis typically is one of exclusions in patients with the appropriate history. Cholesterol embolization can manifest with fever, skin lesions and high eosinophil counts. The differential

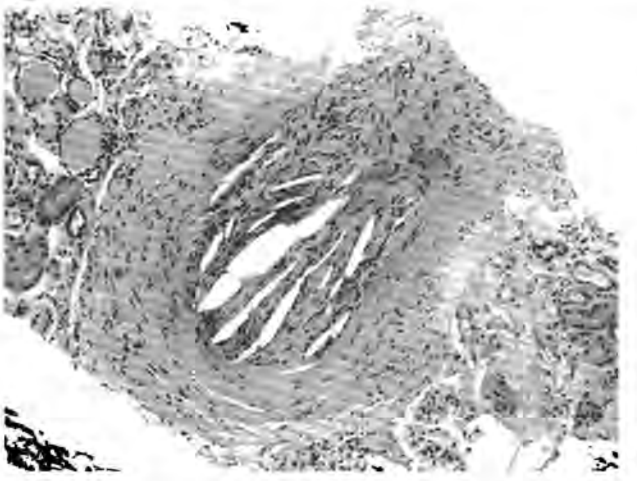


Figure 4: Histologic section of a needle biopsy of the kidney (Hematoxilin-Eosin stain) shows an arteriole with cholesterol embolization in organizing phase. The complete vascular occlusion is mostly by fibrotic tissue. Notice the intraluminal clefts that remain after the embolized cholesterol crystals dissolved during histologic processing. Earlier phases of the disease can demonstrate hystiocytic and giant cell reactions (*For color version, refer to plate 1*)

diagnosis includes hypertensive nephrosclerosis, contrast nephropathy and glomerulonephritis. The only definitive diagnosis is histologic. When related to RAS intervention, there is no specific treatment.

Deterioration of kidney function occurs in a substantial minority of patients receiving angioplasty or stent for RAS. In patients with increased creatinine (serum creatinine >133 μmol/l or >1.5 mg/dL) that receive stenting, renal function can be expected to improve in 25 percent, stabilize in about 50 percent and deteriorated in 25 percent. Stenting may precipitate dialysis in 2 to 3 percent. Patients with normal baseline creatinine manifest deterioration much less frequently, probably because loss of >50 percent of function is needed before creatinine elevation occurs. At first glance this high rate of deterioration is surprising because stability or improvement of function is a reasonable expectation after improvement of renal perfusion. It has been determined that at least in part the deterioration is the result of cholesterol or atheromatous embolization. Duplex ultrasound of the renal artery during endovascular intervention commonly shows microembolic signals. When embolic protection devices are used thousands of microscopic embolization particles are usually recovered. The embolic material is composed of fibrin particles, platelet rich thrombi and atheroma.

The RESIST trial was aimed at determining whether an embolic protection device, platelet inhibition with the glycoprotein IIb/IIIa inhibitor abciximab, or combination treatment improved renal function. Preprocedural abciximab reduced embolization from 42 to 8 percent (P = 0.02). Abciximab decreased the rate of platelet rich emboli (but not atheroma or fibrin emboli) and correlated with better renal function at one month.

Restenosis

Recurrence of the renal artery obstruction can happen after both angioplasty and stenting. Restenosis is a reflection of the normal healing process of arteries subjected to the controlled injury induced by balloon dilatation and stenting. Histologically, the tissue growing into the arterial lumen is described as neointimal hyperplasia, the end result of a cascade of events that is initiated immediately with platelet deposition. Various mechanisms incite cells to proliferate, to deposit matrix, and to promote migration or cellular differentiation into smooth muscle cells.

Compared to angioplasty alone, stents achieve a greater degree of arterial diameter enlargement (acute gain) and have less late loss of lumen. Indeed, larger vessels and greater acute gain in lumen diameter predict less restenosis. Renal arteries with a diameter <4.5 mm and >6 mm have restenosis rates of 36 percent and 6.5 percent, respectively. The restenosis rate for angioplasty can be as high as 50 percent, and the technical success rate and primary patency are inferior to stenting. Stent placement has a statistically significant superiority over balloon dilatation in technical success (98 percent versus 77 percent) and restenosis rate (17 percent versus 26 percent). At five years the primary and secondary patency rates for renal stenting are 85 percent and 93 percent.

Treatment of neointimal hyperplasia after angioplasty or in-stent restenosis includes balloon dilatation, placement of bare metal stents, stents covered with polytetrafluoroethylene graft material (stent graft), cryoplasty or intravascular brachytherapy. A promising option is the use of drug-eluting stents but data are scant and the use of these devices will require validation for cases of restenosis.

Outcome of Renal Artery Stenosis Revascularization

Proving the case for endovascular treatment of RAS with clinical trials of renal artery intervention has been problematic. Because of advances in diagnostic methods, and the widespread availability and relative safety of endovascular therapy compared to surgical revascularization, there has been a large increase in procedures performed but with a weak foundation when data from randomized studies is considered.

There are numerous limitations that can explain the inability of clinical trials to demonstrate outcome differences between medical therapy and revascularization. It appears that severe stenoses and severe clinical cases may be under represented in randomizations, ACE inhibitors or ARB medications may be under utilized in the trials, the definition of outcome measurements vary, the follow up is short, and there are a number of confounding factors that limit the ability to interpret data. A particularly problematic feature of the clinical trials is the high rate of therapeutic crossover form medical to interventional treatment, which results in dampening of the differences between the treatment arms. The definition of a significant stenosis in many trials may not be stringent enough and can interfere with the selection of the population that has the most to gain from intervention. The mixing of mild cases of RAS with those affected severely can mask the benefit of revascularization for the severe group. One must not forget that procedural complications, such as atheroembolism, can negate the benefits of intervention and contribute to the generally disappointing outcomes of the trials.

Uncontrolled trials of endovascular treatment in the 1990s suggested a cure rate for hypertension of 20 percent and improvement in approximately 50 percent; therefore about 70 percent had a blood pressure improvement. Renal function improved in 30 percent and stabilized in approximately 40 percent. Based on the favorable outcomes and good safety and technical success profile of stenting, the application of this procedure became widespread.

After the initial experience with angioplasty and stenting several controlled trials were conducted, but were unable to conclusively demonstrate a blood pressure or kidney function benefit of revascularization over medical therapy. Moreover, the reduction in dose and number of medications after revascularization has been found to be too small for improvement in quality of life to be detectable.

Important trials that have been conducted will not be reviewed in detail. These include the Scottish trial that compared angioplasty versus medical therapy, the EMMA trial that compared angioplasty with or without stent versus medical therapy, the Dutch DRASTIC trial that compared angioplasty versus medical therapy, and the ASTRAL trial that compared angioplasty with or without stent versus medical therapy. These trials concluded that there is no blood pressure benefit for revascularization when compared to medical therapy, a result that led to much discussion. Among the criticisms are the inclusion of small patient populations, selection bias, inclusion of many lesions less than 70 percent (and even less than 50 percent). Other issues are a high likelihood of nonparticipation in the randomization, exclusion of patients with the most severe stenoses, stenosis in solitary kidneys or bilateral lesions, technically questionable stent placements that had a residual narrowing >50 percent, and complication rate were higher than reported in other studies.

The STAR trial, a multicenter European study specifically designed to evaluate the effect of revascularization on kidney function, concluded that a conservative approach should be favored because stenting with medical treatment had no clear positive effect and was associated with complications. The study was seriously flawed by inclusion of stensoses that proved to be mild and stenting was not indicated, it was underpowered, patients with medically resistant hypertension were excluded, and the likely occurrence of selection bias of not offering randomization to the most severe cases. The CORAL trial is an ongoing study of patients with atherosclerotic RAS that compares optimal medical therapy alone versus stenting, embolic protection, and optimal medical therapy, but the results are not yet available. Studies that compared medical therapy versus surgical revascularization, angioplasty without stent versus surgery, and angioplasty with or without stent versus surgical intervention failed to show a clear superiority of surgery to either medical therapy or percutaneous treatment.

Emerging Techniques

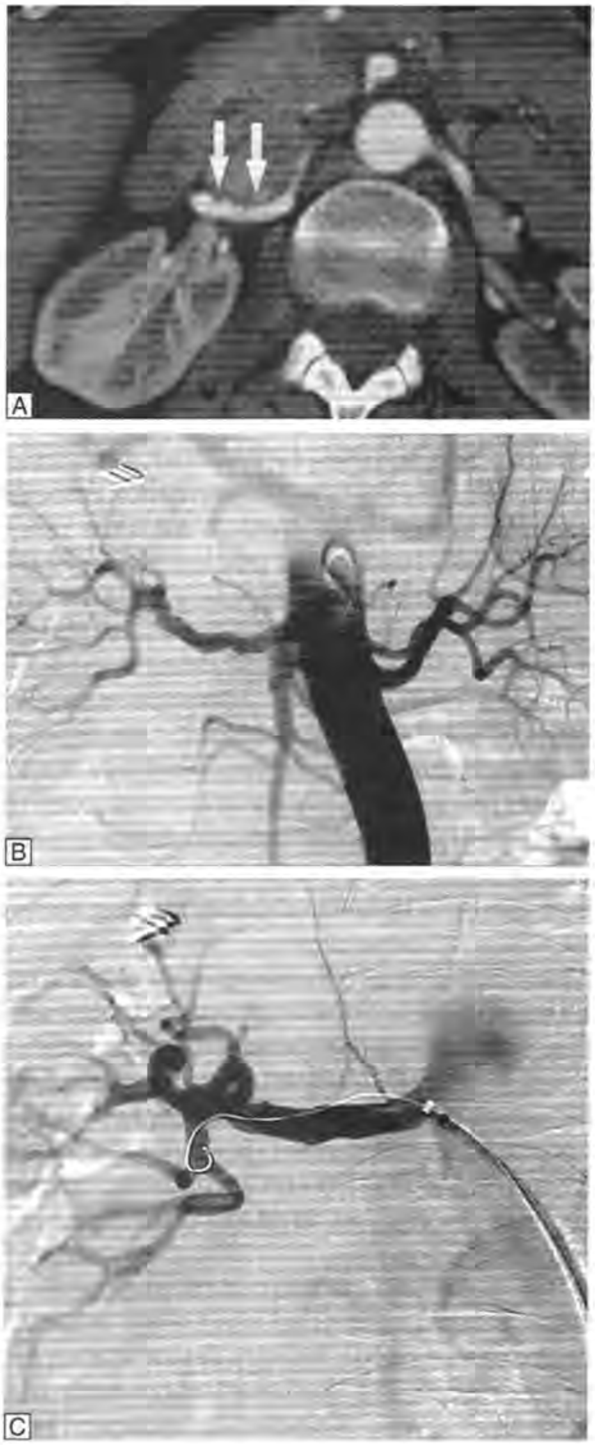
Lumbar sympathectomy can effectively decrease blood pressure in cases of malignant hypertension related to renovascular disease. This procedure is rarely performed today as a result of improvements in medical therapy, the problems related to a major surgery, and side effects such as postural hypotension and bladder, bowel and erectile dysfunction. Recently a new technique of sympathetic denervation has emerged. The procedure utilizes a radiofrequency ablation electrode placed in the renal artery through selective catheterization. Preliminary experience indicates the procedure is safe and can produce durable improvement in systolic and diastolic blood. Norepinephrine overflow from the kidneys is reduced, confirming renal sympathetic denervation. Clinical trials are now indicated.

FIBROMUSCULAR DYSPLASIA

FMD deserves a separate discussion. It can cause severe stenosis of the renal arteries, but with a pathologic basis, physiology, epidemiology, clinical manifestations and response to therapy different from atherosclerotic RAS.

Histologically, FMD is not associated with atherosclerosis and it is not in the spectrum of vasculitis. The pattern will depend on the part of the arterial wall affected. The most common is medial fibroplasia, followed by perimedial fibroplasia, and intimal fibrodysplasia the least common. The typical "string-of-beads" angiographic appearance is seen in medial fibroplasia and can cause severe stenoses. Intimal involvement tends to produce smoothly tapering narrowing. Whereas atherosclerosis is predominantly disease of the proximal renal artery, FMD commonly extends well into the main renal artery and often involves segmental branches. The diagnosis is possible with CTA and MRA, but angiography is confirmatory and sometimes the only technique capable of demonstrating the disease. FMD is classically described in young females and can have a familial tendency. The lesions can be asymptomatic or can cause severe hypertension. In contrast to atherosclerosis, FMD does not cause renal function loss.

Treatment is initiated with antihypertensive drugs, and work up for secondary causes of high blood pressure follows when the response is unsatisfactory. Once FMD is documented revascularization is considered. Although surgery can be effective, the treatment of choice is balloon angioplasty (Figs 5A to C). Stent placement is rarely necessary. Most practitioners find that angioplasty is advantageous because it is minimally invasive, repeatable, less expensive than surgery, more widely available, and can treat into the segmental branches that surgery usually cannot address.



Figures 5A to C: Axial source image (A) from computed tomography angiogram of the abdomen in a 42-year old female with several years of hypertension demonstrated an irregular, beaded appearance of the right renal artery as a result of fibromuscular dysplasia (arrows). Conventional angiography (B) confirmed the diagnosis. Angiography after balloon angioplasty (C) showed a widely patent arterial lumen

KEY POINTS

1. Atherosclerotic RAS is the most common cause for renovascular disease. FMD is less common but an

important etiology with pathology, clinical features and response to therapy that generally differ from atherosclerosis.

2. Revascularization for RAS intends to improve hypertension, stabilize or improve renal function, and improve unstable cardiac syndromes of angina and congestive failure.
3. Angiographic renal artery diameter reduction greater than 70 percent, or development of a pressure gradient across the stenosis of at least 10 to 20 mmHg, is necessary for increased secretion of renin.
4. The pathophysiology of renovascular hypertension and ischemic nephropathy is complex. This complexity explains the wide variability in clinical response to revascularization.
5. Imaging is essential in the diagnostic work up for renal artery stentosis. Ultrasound reflects hemodynamics with limited anatomic detail, while computed tomography and MRA provide detailed anatomic information.
6. Revascularization should be considered if there is progressive decline in GFR during treatment of systemic hypertension, failed medical therapy for hypertension, GFR deterioration while on ACE inhibitors or ARBs, or recurrent congestive heart failure in a patient in whom the adequacy of left ventricular function does not explain the degree of failure.
7. Balloon angioplasty, stenting and surgical revascularization are all valid interventions in properly selected patients, but stenting is overwhelmingly the most commonly performed procedure.
8. Participating populations in various clinical trials of revascularization for RAS have not conclusively demonstrated a benefit, but individual patients can greatly benefit from revascularization.

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SECTION 5

GLOMERULAR DISEASE

- Poststreptococcal Glomerulonephritis
- Nephrotic Syndrome
- Tuberculosis of the Kidney

30 Poststreptococcal Glomerulonephritis

JP Tiwari, Kedareshwar PS Narvencar

Acute poststreptococcal glomerulonephritis (APSGN) occurs as postinfectious nonsuppurative, immunologically mediated sequelae to infection with group A beta hemolytic streptococci. WHO estimates that over 4,70,000 cases of APSGN occur annually, 97 percent in underdeveloped countries. The disease is more common in children than adults. The incidence of the disease varies in different regions, developing world having a higher incidence than developed world, for instance 24.3 per 1,00,000 in underdeveloped countries and 2.0 per 1,00,000 in more developed countries.

The mortality from APSGN is less than 0.5 percent. Less than 2.0 percent of patients go on to develop end stage renal disease, and most of the deaths and cases of chronic disease occur in adults.

PATHOGENESIS

APSGN occurs following upper respiratory tract infection with group A Streptococci (GAS) in colder climates and following Streptococcal skin infections in warmer climates. While streptococcal pharyngitis is known to cause rheumatic fever by similar mechanisms as that of glomerulonephritis, the strains causing rheumatic fever do not cause APSGN. Group A streptococci are generally classified based on surface M proteins. However, they can also be classified into two groups based on the presence or absence of a lipoproteinase that causes serum to become opaque (serum opacity factor). The opacity factor positive groups contain nephritogenic strains while opacity factor negative groups are generally rheumatogenic. Rarely group C and G streptococci also cause glomerulonephritis.

Various streptococcal factors implicated in the pathogenesis of APSGN involve:

1. Streptococcal M protein
2. Autoimmunogenic streptococcal-altered immunoglobulins
3. Endostreptosin and pre-absorbing antigen (PA-Ag)
4. Streptococcal pyrogenic exotoxin B (SpeB)
5. Cationic antigens
6. Streptokinase

Host Factors

Host factors responsible for APSGN are not completely elucidated. Overcrowding, poor hygiene, malnutrition, anemia, parasite infestations, alcoholism predispose patients to a higher risk of developing APSGN.

Males are affected more than females in the ratio of 2:1. This is probably due to some genetic predisposition in males to develop immunological reaction to the infectious agent.

Pathogenic Mechanisms

APSGN occurs secondary to immune complex formation. Serum complement factors C3 and C5 are reduced during the acute phase in almost all APSGN patients and usually return to normal within six weeks, thus supporting the immune complex formation. The various theories proposed on the mechanism by which immune complexes cause APSGN are:

1. Glomerular trapping of circulating immune complexes
2. In situ immune complex formation resulting from antibodies reacting with either streptococcal components deposited in the glomerulus or with

components of the glomerulus itself ("molecular mimicry"). This initiates inflammatory reaction by activation of complement via alternative pathway. This leads to deposition of C_3 recruitment of immune cells, tissue destruction, IgG deposition, and further aggravation of the inflammatory reaction. Antibodies against glomerular basement membrane components, such as laminin and type IV collagen are demonstrated in the sera of patients with APSGN. The antigenic determinant for initiating cross-reactivity with human glomerulus is the tetrapeptide near the amino terminus of type one streptococcal M protein.

3. Streptococcal proteinase or streptococcal pyrogenic exotoxin B (SPEB). Antibodies to SPEB have been documented to rise in sera of patients with APSGN in the acute phase which persists even up to one year after the disease.
4. Anti-immunoglobulin activity of streptococcal components.
5. Glomerular plasmin binding activity of streptococcal components.

Immune complex deposition leads to recruitment of various inflammatory cells, which lead to tissue damage. Release of C5a upon complement activation, cytokine production by phagocytes and membrane attack complexes contribute to these processes.

Adhesion molecules are responsible for this infiltration of leukocytes. Leukocyte adhesion to endothelium occurs in two steps: in the first step, interaction between selectins and carbohydrate ligands lead to rolling of leukocytes on the endothelium. In the second step, there is interaction between leukocyte integrins and endothelial immunoglobulin like molecules such as ICAM 1 and VCAM 1 which leads to leukocyte immobilization. A similar mechanism also leads to interstitial leukocyte infiltration.

Apoptosis exists in the glomerulus from acute to late stages of APSGN, which is responsible for the resolution of hypercellularity and thereby resolution of the disease.

PATHOLOGY

The disease is characterized by enlargement of glomeruli with hypercellularity. The hypercellularity is due to two reasons:

1. Proliferation of resident mesangial cells as well as endothelial and epithelial cells
2. The infiltration of leukocytes. The leukocytes most commonly identified are neutrophils (exudative glomerulonephritis); however monocytes and macrophages also infiltrate.

The hypercellularity is usually diffuse. Various morphological changes seen include occlusion of capillaries, lobulation of the glomerular tuft, adhesions (synechiae) between the tuft and the capsule and sometimes crescent formation.

In the early stage of the disease, there is deposition of C3 in the glomerulus and later of IgG. Based on the pattern of deposition of C3 and IgG, various patterns are described.

1. **'starry sky pattern'**. This corresponds to irregular and finely granular C3 and IgG deposition along the glomerular capillary walls and in the mesangium. It is commonly seen in the early stages of the disease.
2. **'mesangial pattern'**. There is deposition of IgG and C3 in the mesangium, generally with a predominance of C3.
3. **'garland pattern'**. Here there is densely packed C3 and IgG deposition along glomerular capillary walls, which appears like a garland on ultramicroscopy. This garland pattern was associated with more numerous and larger subepithelial "humps" and higher degrees of proteinuria. C3 deposition is more intense than that of IgG, and C3 has also been detected without concomitant IgG deposition. Properdin, a component of the alternative pathway of the complement cascade, has been detected in glomeruli in the early, but not late, convalescent stage of APSGN.

CLINICAL FEATURES

APSGN is usually a disease of childhood occurring commonly in the age group of six to eight years. It is rare before the age of two years.

The disease presents through three phases, latent phase, acute phase and recovery phase. After a latent phase of one to three weeks of a throat infection or three to six weeks after a skin infection, the patient with APSGN typically presents with proteinuria (usually of non nephrotic range), microscopic or gross hematuria, RBC casts, hypertension, oliguria, edema and back pain. Hematuria is described by the patient or family as tea-colored or cola-colored urine. Patients may rapidly progress to develop rapidly progressive (crescentic) glomerulonephritis with worsening renal function. They may also develop hypertensive crisis leading to hypertensive encephalopathy. Some patients develop volume expansion, heart failure and pulmonary edema.

Atypical presentations may be seen in some patients. These include Henoch-Schönlein purpura rash, subclinical disease or acute presentation secondary to hypertensive complications without obvious urinary abnormalities.

During the recovery phase, hypertension usually settles within one to two weeks, usually without treatment along with resolution of fluid overload. Proteinuria subsides earlier than hematuria. C3 levels return to normal.

Laboratory Abnormalities

Urinary abnormalities dominate the picture. Urine routine examination reveals presence of dysmorphic red blood cells and leukocytes; red blood cell and white blood cell casts. Proteinuria is usually in the nephritic range; however in some it may progress to nephrotic range.There is rise in blood urea nitrogen and serum creatinine.

Serological markers used include elevated antistreptolysin O (ASO) titer and depression of serum C3 level. Increased antibody levels to antistreptococcal antigens [ASO, antihyaluronidase (A-H) and antiDNAase] are documented less often. Renal biopsy is usually not indicated except when the diagnosis is in doubt or in the setting of crescentic glomerulonephritis.

DIFFERENTIAL DIAGNOSIS

1. Primary renal glomerular disorders (e.g., membranoproliferative GN, IgA nephropathy),
2. Collagen vascular diseases (systemic lupus erythematosus),
3. Systemic vasculitis (Henoch-Schonlein purpura)
4. Hereditary nephritis
5. Some nonglomerular conditions.

Treatment

Treatment is usually supportive. Hypertension is treated with antihypertensives, initial choice being loop diuretics. Fluid overload is the main contributor to hypertension, hence salt restriction is useful. If hypertension persists despite this treatment, other agents such as vasodilators are used. Dialysis may be indicated if the fluid overload does not subside despite salt restriction and the use of diuretics.

There is no consensus on whether treatment of streptococcal infection can prevent development of APSGN. In communities where APSGN is highly endemic, treatment of the community with benzathin penicillin may help reduce the incidence of APSGN.

Immunosuppressive therapy is not indicated except in the setting of crescentic glomerulonephritis or rapidly progressive glomerulonephritis.

Prognosis

Excellent in children. Complete recovery is the rule. Microscopic hematuria may persist but has no impact on renal function. On the contrary, in adults, proteinuria may persist for some time but, again, has very little impact on recovery of kidney function.

KEY POINTS

1. Poststreptococcal glomerulonephritis is a sequelae to group A beta hemolytic S streptococci.
2. It occurs commonly in children mostly in underdeveloped countries where there is crowded living and personal hygiene is poor.
3. It manifests severely in children with gross hematuria, edema, and acute renal failure.
4. Hypertension, hypertensive encephalopathy may occur.
5. It is a self-remitting disease but requires symptomatic treatment, such as control of hypertension. Loop diuretic is the choice of therapy.
6. Residual effects or progression to chronic renal failure is rare in children but may be found in adults.
7. Prophylaxis with penicillin or erythromycin may prevent recurrent infection.

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Nephrotic Syndrome

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DEFINITION

Nephrotic syndrome is characterized by proteinuria greater than 3.5 gm/1.73 m^2 of body surface area/day, along with hypoproteinemia, edema, dyslipidemia, and various metabolic derangements secondary to proteinuria and hypoproteinemia. Nephrotic syndrome may be either primary or secondary to other systemic diseases. However, this classification is arbitrary as there is a significant overlap between the two types (Table 1). The constellation of signs and symptoms of this syndrome results from the loss of large amounts of protein in the urine.

PATHOGENESIS

1. Role of T cells: The pathogenesis is thought to be secondary to immune dysregulation involving cell mediated immunity. This hypothesis is supported by the occurrence of minimal change nephrotic syndrome (MCNS) after a viral infection or an atopic disorder. The disease is seen in association with HLA antigens and with non-Hodgkin's lymphoma, which also substantiates this view. Expansion of CD4+ and CD8+ T cell populations is seen in MCNS, which may be responsible for the immune dysregulation.

   Another hypothesis is the involvement of Th2 cytokine bias. A defect in delayed type hypersensitivity reaction is often seen in patients with MCNS, which substantiates this hypothesis. This hypothesis suggests that Th2 helper CD4+ secretes predominantly IL 4, which binds to its respective receptors on podocytes, thereby altering the basement membrane permeability and leading to protein loss. During relapse, a selective Th2 specific factor c-maf is induced.
2. Hypogammaglobulinemia: It is seen that there is decreased production as well as increased catabolism of IgG in minimal change disease as well as in other types of nephrotic syndrome. Further, there is a difference between various IgG subclasses; circulating levels of IgG1 and IgG2 are profoundly depressed and their in vitro synthesis impaired, but IgG3 and IgG4 subclasses are relatively spared.
3. Circulating factors: Another pathological mechanism suggested in MCNS and focal and segmental glomerulosclerosis (FSGS) is of a systemic circulating factor, such as vascular endothelial growth factor (VEGF), heparanase, and hemopexin, which increases glomerular permeability.
4. Transcription factors and proteasome activity: High NFkB activation in CD4+ T cells is observed during the relapse of nephrotic syndrome. The abnormal activities of such transcriptional factors may be responsible in the pathogenesis of the disease. Podocytes also express various receptors, which may also be playing a role.
5. Alteration of other immune cell subsets in MCNS:
6. Several transcriptional and post-transcriptional mechanisms of various genes (such as GATA3 in regulation of nephrin gene expression) contribute to the immunological disorders in MCNS.

Edema

This is the most common symptom in patients with nephrotic syndrome. Though the primary cause of edema is hypovolemia secondary to reduced plasma

Table 1. Etiology of nephrotic syndrome

Primary --- idiopathic
Secondary
Neoplasia
Hematological
_ Hodgkin's disease
_ NonHodgkin's lymphoma
_ Leukemia (chronic lymphocytic, intravascular lymphoma) multiple myeloma and amyloidosis
_ Waldenstrom's macroglobulinemia
_ Angiofollicular lymph node hyperplasia
_ Lymphoid hamartoma
Solid tumors
_ Thymoma (with or without myasthenia gravis)
_ Renal cell carcinoma
_ Mesothelioma
_ Bronchogenic carcinoma
_ Colon carcinoma
_ Pancreatic carcinoma
_ Urothelial cancer
_ Prostatic carcinoma
_ Renal oncocytoma
_ Wilms tumor
Drugs
Gold
Organic/inorganic/elemental mercury
Antimicrobials (ampicillin, rifampicin, cefixime)
NSAIDs (ibuprofen, fenoprofen, piroxicam, diclofenac, tolmetin, naproxen, zomepirac, indomethacin)
Enalapril/captopril
Penicillamine
Probenecid
Lithium
Interferon (α, β)
Trimethadione
Tiopronin
Paramethadione
Methimazole
Tamoxifen
Warfarin
Contrast media
Illicit drugs like heroin
Immunizations-- tetanus-diphtheria-pertussis-vaccination
Infections
Viral--- Human Immunodeficiency Virus, influenza, hepatitis B and C, Epstein Barr virus, CMV.
Bacterial—infective endocarditis, PSGN, shunt nephritis, Mycoplasma,Tuberculosis, Syphilis
Parasitic—Malaria, toxoplasmosis
Helminthic—Ehrlichiosis, Echinococcus (hydatid disease), Schistosomiasis, trypanosoma
Atopy
Pollen
Snake venom
Dairy products (milk)
House dust
Pork
Bee stings
Poison oak/ivy
Superimposed on another renal disease/multisystem disorders
IgA nephropathy/ Henoch-Schönlein purpura
Systemic lupus erythematosus
Rheumatoid arthritis
Goodpasture's syndrome
Sjögren syndrome
Diabetes mellitus (new onset type 1)
Autosomal dominant and recessive polycystic kidney disease
HIV associated nephropathy
Miscellaneous
Sclerosing cholangitis
Sclerosing mesenteric inflammation
Vigorous exercise
Severe/malignant hypertension
Acute decompression sickness
Sarcoidosis
Grave's disease
Thyroiditis
Pregnancy associated—ecclampsia, pre-eclampsia
Vasculitis
Sickle cell disease
Spherocytosis
Storage disorder
Alport syndrome
Fabry disease
Partial lipodystrophy
Myasthenia gravis (without apparent thymoma)
Renal artery stenosis
Bis-albuminemia
Guillain-Barre syndrome
Dermatitis herpetiformis
Melorheostosis, mesenteric fibrosis, hemangiomas
Chronic graft versus host disease (post hematopoietic stem cell transplantation)

Contd...

albumin, primary renal defect is postulated to be a cause by certain investigators. The lesion in nephrotic syndrome is thought to involve not only the glomerulus but in addition may also have tubular lesion leading to excessive reabsorption of sodium.

"Underfill" Hypothesis

This is thought to be the main cause of edema in nephrotic syndrome. Proteinuria results in hypoalbuminemia, which leads to reduced plasma oncotic pressure. This is perceived by kidney glomerulus as hypovolemia. The resultant activation of various mechanisms, such as renin-angiotensin-aldosterone system, sympathetic nervous system, and vasopressor system, lead to avid sodium and water retention leading to edema.

"Overfilled" Hypothesis

Pathophysiology of edema in adults with nephrotic syndrome is more complex. The patients have hypertension or expanded plasma volume in addition to expanded interstitial volume. In this situation, the edema occurs secondary to primary renal mechanism. These patients have tubulointersitial disorder in addition to glomerular pathology, which leads to increased tubular reabsorption of sodium resulting in edema. Even in children, the edema cannot be explained by hypovolemia alone; primary renal retention of sodium contributes to it. These patients, therefore, develop pulmonary edema if albumin infusions are given to them.

The basic pathophysiological mechanism is that of enhanced sodium reabsorption along the cortical collecting ducts and a blunted natriuretic response of medullary collecting ducts to atrial natriuretic peptide. Induction of de novo synthesis of Na,K-ATPase is the primary effector of this mechanism. The sodium retention leads to asymmetric expansion of interstitium owing to changes in intrinsic properties of the capillary endothelial barrier. This leads to the development of edema.

Management of Edema

The goal of treatment should be to have a slow resolution of edema. Rapid diuresis should be avoided as it would lead to hypovolemia and resultant hypotension. Dietary restriction of sodium and use of natriuretic drugs that target collecting duct, such as amiloride, is useful in limiting sodium accumulation. In patients with significant edema, excretion of accumulated sodium and fluid can be achieved with the use of diuretics such as thiazides, and, in severe edema, loop diuretics. Metolazone may be effective when used in combination with loop diuretics. During diuretic therapy, clinician should be vigilant for profound volume depletion, which will lead to hypovolemia and renal insufficiency. Cessation of diuretic therapy and effective rehydration will be sufficient to revert this.

Albumin infusions are useful in patients with hypoproteinemia and profound volume depletion. However, this is a temporary measure as the infused albumin will be excreted within 48 hours.

In patients with refractory edema and in cases of associated renal insufficiency, extracorporeal dialysis may be useful.

Hyperlipidemia

This is another sentinel feature of nephrotic syndrome. There are various mechanisms responsible for this.

a. Increased hepatic lipoprotein synthesis consequent to fall in plasma oncotic pressure
b. Decreased catabolism of individual lipid fractions such as triglycerides, LDL and lipoproteins

The various lipid abnormalities that occur in nephrotic syndrome are listed in Table 2.

While in steroid sensitive MCNS, hyperlipidemia is transient and does not cause any long-term sequelae; in steroid resistant nephrotic syndrome, it is persistent and may result in cardiovascular morbidity and progression of glomerulosclerosis.

The patients should be advised on dietary restriction of saturated fats to reduce hyperlipidemia. Short-term efficacy of statins (HMG-CoA reductase inhibitors) has been demonstrated, but there are no standard guidelines regarding their use. As mentioned above, in steroid-sensitive nephrotic syndrome, hyperlipidemia is transient and, hence, does not require any medications. In steroid resistant nephrotic syndrome, therapy with statins is indicated in those patients in whom hyperlipidemia (total cholesterol >200 mg/ dL, LDL cholesterol >130 mg/dL and triglycerides >200 mg/dL) persists for three to six months despite specific treatment for nephrotic syndrome. Bile acid sequestrants and fibrates may be used, especially in children where safety of statin use is not conclusively proven.

Table 2. Lipid abnormalities in nephrotic syndrome

- Increased lipoprotein synthesis
- Increased cholesterol
- Increased LDL
- Increased triglycerides
- Low HDL
- Decreased metabolism of lipoprotein lipase and lecithin cholesterol acetyltransferase
- Increased transport of Apo B-100

Table 3. Coagulation abnormalities in nephrotic syndrome

- Increased plasma fibrinogen
- Increased factors II, V, VII, VIII, X, XIII
- Decreased factors IX, XI, XII
- Decreased antithrombin III, protein S (secondary to urinary loss)
- Decreased plasminogen
- Increased platelet aggregability

Thromboembolic Events

Nephrotic syndrome patients are at a higher risk of developing arterial and venous thrombosis. While in children with MCNS, the risk is 2 to 8 percent; in adults, it is much higher. Various mechanisms are responsible for that. Nephrotic syndrome patients have several coagulation abnormalities (Table 3), which predispose them to thromboembolic events. Volume depletion, infections, diuretic use, venepuncture, and immobilization aggravate the risk.

Patients with proven thrombosis should be treated with either unfractionated heparin or low molecular weight heparins. The latter is preferred due to the ease of administration, but not used in patients with impaired renal function. This should be followed by the maintenance therapy with warfarin for at least a period of six months. Prophylactic use of anticoagulants is not recommended at present.

Other Consequences of Proteinuria

Endocrine and Metabolic Abnormalities

a. Urinary loss of thyroid binding globulin and T_4 results in low free and bound T_4 and low total T_3. However, most patients remain functionally euthyroid. Corticosteroid therapy further alters the thyroid hormone profile.
b. Loss of Vitamin D binding protein may lead to altered calcium and vitamin D levels; however, bone mineralization remains unaffected. Further alterations in calcium homeostasis occur due to prolonged corticosteroid therapy.
c. Loss of immunoglobulins and complements lead to increased susceptibility to infections.
d. Loss of transferrin and erythropoietin leads to anemia.

Complications

1. Infection: Spontaneous peritonitis is the most common infection, which is followed by cellulitis, pneumonia, and viral upper respiratory tract infections . There are various reasons for increased predisposition to infection, which include loss of immunoglobulins, complement, and properdin in urine. In addition, altered T cell function and edema contribute to infections. Various preventive modalities have been proposed, but their efficacy is doubtful. These include intravenous immunoglobulins, vaccination against capsulated organisms, and prophylactic oral antibiotics.
2. Thromboembolic events
3. Hypertension
4. Hyperlipidemia
5. Osteoporosis
6. Treatment-related toxicity

CLASSIFICATION

Congenital Nephrotic Syndrome

This is defined as the nephrotic syndrome occurring in children during first three months of age. The etiology of this disorder is varied. A similar disease can occur at a later age when it is defined as either infantile (between ages 4 to 12 months) or childhood nephrotic syndrome (after 1 year of age). In majority of the patients, the disease is caused by mutations in genes, which encode structural and functional proteins of renal filtration barrier. Experimental studies in mice have demonstrated that the loss of podocyte gene may cause nephrotic syndrome. In the remainder, it is caused by nongenetic factors, such as congenital syphilis, HIV, malaria, maternal SLE, etc.

The diagnosis of congenital nephrotic syndrome is established by generalized edema, proteinuria exceeding 20 gm/L and serum albumin <1 gm/L occurring in the neonatal period. Clinical signs may not be evident in early weeks of life. The magnitude of proteinuria may also vary. Blood urea and creatinine may rise as renal failure progresses. Hypertension occurs when there is renal failure. Genetic analysis is the investigation of choice in the diagnosis of etiology. In families with known mutations, prenatal diagnosis should be done.

Management of Congenital Nephrotic Syndrome

Steroids or immunosuppressive therapy are not useful in achieving remission in congenital nephrotic syndrome. The goals of therapy, are symptomatic which include control of edema and hypoalbuminemia, prevent uremia, and prevent and treat complications (such as infections and thrombosis), and also provide adequate nutrition for the growth and development of the child. The curative treatment is renal transplantation. Edema can be controlled by IV infusions of salt free albumin with or without loop diuretics, high dietary protein intake (4 gm/day), and controlling urinary loss of proteins by medications, such as calcium channel blockers.

Minimal Change Nephrotic Syndrome

MCNS is a clinical and pathological entity defined by selective proteinuria and hypoalbuminemia that occurs in the absence of cellular glomerular infiltrates or immune deposits. The primary pathology involves the epithelial visceral cells (podocytes) with effacement of the foot processes. This type occurs predominantly in children. Though primarily, it is idiopathic; in a small proportion of patients, underlying disorder, such as systemic lupus erythematosus, Henoch Schonlein purpura, amyloidosis, infection with HIV, parvovirus B19, and hepatitis B and C viruses, and drugs, such as gold, penicillamine, NSAID, interferon, may be identified.

Pathology

Light microscopically, minimal change disease has no glomerular lesions. On immunofluorescence microscopy, there is no staining of glomeruli for IgG, IgM, IgA, C3, C4, and C1q. The striking feature is the low level of mesangial staining for IgM and C3. Electron microscopy shows effacement or total fusion of visceral epithelial cell foot processes and microvillous projections of epithelial cytoplasm.

CLINICAL FEATURES

There is an abrupt onset of heavy proteinuria along with generalized edema, hypoalbuminemia, and hyperlipidemia. The presenting feature in most patients is that of lower extremity edema, weight gain, and fatigue. Therefore, nephrotic syndrome should be one of the differential diagnoses in any patient presenting with a new onset edema. In advanced cases, there may be periorbital edema, ascites, pleural and pericardial effusion. Hematuria is unusual. Though hypertension is not a common feature in children, adults with minimal change disease may present with hypertension.

In adult patients, there may be associated acute renal failure. Contributing factors for renal failure include older age, severe edema or proteinuria, excessive diuresis, therapeutic drug complications, sepsis, renal venous thrombosis, renal interstitial edema, marked hypotension and atherosclerotic renal vascular disease.

In drug-induced minimal change disease, patients have pyuria in addition to proteinuria due to associated tubulointerstitial disease. On discontinuation of the offending drug, such as NSAID there is usually resolution of the disease; however, this may take many months.

Laboratory Findings

Nephrotic range proteinuria is the main laboratory finding in minimal change disease. Microscopic hematuria is found in a minority of patients. Hypoalbuminemia and hyperlipidemia are common. Owing to severe hyperlipidemia, there may be pseudohyponatremia. Renal function is usually normal in minimal change disease.

TREATMENT

Corticosteroid is the usual modality of treatment for MCNS. Seventy percent of children go into remission within two weeks of steroid therapy. However, 75 percent of them relapse after stopping steroids. About half of these patients are frequent relapsers. Factors predicting frequent relapses include, age younger than three years at onset, delayed time to remission (after seven to nine days), and occurrence of an early relapse (in the first six months after initial treatment).

Treatment of Initial Episode

Definitions of responses to treatment will be found in Table 4. Appropriate treatment of the first episode is important as this determines the chronic course of the disease.

The initial episode is treated with steroids, either prednisone or prednisolone. Therapy is started with a daily dose of 2 mg/kg in single or divided doses in children (maximum of 60 mg/day) for a period of six weeks followed by 1.5 mg/kg/day (maximum 40 mg/day) as a single morning dose on alternate days for next six weeks. For adults, the dose is 1 mg/kg/day (maximum of 80 mg/day) for initial six weeks followed by alternate day therapy for next six weeks. Steroid taper is not required at the end of this therapy. A 24-month sustained remission rate of 49 percent and frequent-relapse rate of 29 percent is expected with this regimen. However, debate regarding prolongation of therapy beyond 12 weeks is ongoing. While most recommendations include discontinuation of therapy after 12 weeks, Cochrane renal group in their review suggested that prolongation of therapy for up to six months was associated with significantly lesser number of relapses.

Treatment of Relapse

Infrequent Relapse

Relapse is treated with steroids in the dose of 2 mg/kg/day in children or 1 mg/kg/day in adults in single or divided doses until urine protein is trace or nil on three consecutive days. The therapy is then continued with alternate day steroids at 1.5 mg/kg as a single morning dose for next four weeks and then discontinued. In case the patient does not achieve remission within two weeks of daily steroid therapy, it may be prolonged for another two weeks. However, if remission is not achieved despite four weeks of daily therapy, alternative treatments should be considered.

Table 4. Definitions of response to therapeutic intervention

Relapse: urine protein 3+ or 4+ or proteinuria more than 40 mg/m^2/hr for 3 consecutive early morning specimens, patient having been in remission previously.

Remission: This is defined as the absence of proteinuria by dipstick analysis for at least 3 consecutive days.

Frequent relapses: two or more relapses in initial 6 months or more than 3 relapses in any 12 months.

Steroid dependence: Two consecutive relapses on alternate day steroids or within 2 weeks of its discontinuation.

Steroid resistance: Absence of remission despite therapy with daily prednisolone of 2 mg/kg/day in children or 1 mg/kg/day in adults for a period of 4 weeks.

Treatment of MCD with low-dose prednisolone and CsA may be as effective as high-dose prednisolone in the remission rate of nephrotic syndrome but is less frequently followed by side effects. However, more research is required before generalized recommendation can be made regarding the combination use.

Frequently Relapsing Nephrotic Syndrome

In cases of frequent relapses or steroid dependence, patient is continued on alternate day steroids at a dose of 0.5 to 0.7 mg/kg for a period of 4 to 18 months. There is no clear data on the total duration of this therapy; therefore, the duration of therapy is empirical based on individual opinion. A close monitoring is required to record the child's growth and identify steroid toxicity at the earliest. If the dose of steroids required to maintain remission is > 0.5 mg/kg on alternate days or if the patient develops steroid toxicity, then one of the following immunomodulators is used. Cochrane renal group, based on meta-analysis of 18 randomized trials, concluded that minimum 8 weeks courses of cyclophosphamide, mycophenolate mofetil or prolonged courses of cyclosporin and levamisole reduce the risk of relapse in children with relapsing steroid-sensitive nephrotic syndrome (SSNS) compared with coricosteroids alone. Choice between these agents depends on physician and patient preferences related to therapy, duration, and the type and frequency of complications. These therapies are:

1. Oral cyclophosphamide: 2 mg/kg per day for 8 to12 weeks (cumulative dose: 168 mg/kg) based on ideal body weight started during prednisone (2 mg/kg per day) induced remission, decrease prednisone dose to 1.5 mg/kg on alternate days for 4 weeks, and then taper over 4 weeks.
2. Mycophenolate mofetil: 25 to 36 mg/kg per day (maximum: 2 g/day) divided into two daily doses (BID) for one to two years with a tapering dose of prednisone.

3. Cyclosporine A: 3 to 5 mg/kg per day divided BID for an average of two to five years.
4. Levamisole: 2 to 2.5 mg/kg on alternate days for 12 to 24 months along with prednisolone 1.5 mg/kg on alternate days for 2 to 4 weeks followed by a gradual taper over next 6 months.

Management of Steroid-Resistant Nephrotic Syndrome in Children

Guidelines on Treatment

1. The Indian Society of Pediatric Nephrology recommends that all children with SRNS, whether initial or late, should undergo a renal biopsy before instituting specific treatment.
2. Based on the systematic review by Cochrane renal group, it is recommended that the patients with idiopathic SRNS—secondary to MCNS, FSGS, and mesangioproliferative glomerulonephritis—should receive similar therapy. While cyclosporin A is demonstrated to be superior to cyclophosphamide in one study, there is no consensus on the superiority of one regimen over other. Therefore, it is recommended that one of the following regimens may be selected based on individual physician preference and/or cost of therapy.
   a. Calcineurin inhibitors with tapering doses of alternate day steroids: Cyclosporin is used in the dosage of 4 to 6 mg/kg/day in 2 divided doses along with prednisolone in the dose of 1.5 mg/kg on alternate days for 4 weeks; 1.25 mg/kg next 4 weeks; 1 mg/kg for 4 months; 0.5 to 0.75 mg/kg for 12 to 18 months. Instead of cyclosporin, tacrolimus may be used as it has better adverse event profile as compared to cyclosporin. Tacrolimus is highly diabetogenic. Therefore, regular glucose testing is essential.
   b. Cyclophosphamide with tapering doses of alternate day steroids: Oral Cyclophoshamide is used in the dose of 2 to 3 mg/kg/day for 12 weeks along with prednisolone in the similar tapering dosage as given above. IV cyclophosphamide is used in the dose of 500 to 750 mg/m^2 once every month for six months along with oral prednisolone in tapering doses.
   c. High-dose intravenous steroids (dexamethasone, methylprednisolone) with oral cyclophosphamide and tapering alternate day steroids: Methyl prednisolone is given in dose of 20 to 30 mg/kg for six alternate day pulses; then once a week for eight doses, fortnightly for four doses, once a month for eight doses; finally bimonthly for four doses; IV dexamethasone, 4 to 5 mg/kg for six alternate day pulses; then every fortnight for four doses; finally once a month for eight doses.
   d. Ponticelli Regimen: IV methylprednisolone along with chlorambucil for six months is found to be very effective in idiopathic nephrotic syndrome.
   e. Mycophenolate mofetil
   f. Levamisole
   g. Use of plasma exchange and immunoabsorption is controversial and, therefore, not routinely advocated.
   h. In adult patients with steroid and mycophenolate mofetil resistant MCNS, there is some evidence of benefit for therapy with rituximab, which will cause beta cell depletion.

Angiotensin Converting Enzyme Inhibitors (ACEI)

ACEI group of drugs have been shown to reduce proteinuria and thereby slow down the progression of renal disease. All patients with SRNS should receive ACEI starting at a low dose and subsequently stepped up provided the GFR is > 30 ml/minute/1.73 m^2. Patients intolerant to ACEI may be put on angiotensin receptor blockers (ARB). ACEI should also be considered in most patients with steroid dependent or frequently relapsing nephrotic syndrome regardless of blood pressure. (See editor's comment.)

Editor's comment: ACEI/ARB drugs are most commonly used to reduce proteinuria. Undoubtedly, proteinuria is reduced, but it happens only at the expense of reduction of GFR. There is no magic mechanism underlying ACEI/ARB drugs to reduce proteinuria. Proteinuria is benign and, by itself, has no consequential effect on renal function.

Statins

Patients with blood levels of total cholesterol >200 mg/dL, LDL cholesterol >130 mg/dL, and triglycerides >200 mg/dL persisting for more than three to six months require therapy with HMG CoA inhibitors (statins) to avoid complications secondary to hyperlipidemia.

Focal and Segmental Glomerulosclerosis (FSGS)

FSGS is one of the main causes of idiopathic nephrotic syndrome in adults. FSGS may be primary (idiopathic or genetic) or may occur secondary to other disorders, such as HIV, sickle cell disease, morbid obesity, cyanotic heart disease, or hypoxic pulmonary disease, or due to drugs, such as lithium or IV drug abuse.

All of the genetic defects identified to date affect gene transcription or assembly of critical podocyte functional structures, such as actin-based cytoskeleton, and adhesion complexes. These genes include nephrin (NPHS1), podocin (NPHS2), alpha-actinin-4 (ACTN-4), CD2-associated protein (CD2AP), Wilm's tumor gene (WT1), and transient receptor potential cation 6 (TRPC6).

Pathophysiology

Pathophysiologically, there is effacement of foot processes of podocytes, leading to distortion of its normal architecture. The connection between the foot processes and underlying glomerular basement membrane is disrupted, leading to protein loss in the tubular filtrate. In addition, histologically, there is deposition of increased extracellular matrix within the glomerular tuft with obliteration of the glomerular capillary lumen. These sclerotic lesions occur focally and in only some segments of glomeruli. They are not associated with immune complex deposition.

Based on the pattern of sclerosis, FSGS is classified as perihilar variant (associated with sclerosis of the vascular pole), cellular variant (associated with hypercellularity of the capillary space), tip variant (sclerosis of the glomerulus near the origin of the proximal tubule), and collapsing variant (with one or more glomeruli with global or segmental collapse).

Immunofluorescence microscopy shows nonsclerotic glomeruli and segments to be devoid of immunoglobulin or complement staining. In a few patients, there may be low level of mesangial staining for IgM in nonsclerotic glomeruli.

Sclerotic glomerular segments have irregular staining for C3, C1q, and IgM, while epithelial resorption droplets stain for plasma proteins. Electron microscopic features of FSGS are nonspecific; but help to exclude other causes of glomerular scarring.

Injury to podocytes occurs by any one or all four mechanisms:

1. Alteration of the components of the slit diaphragm or interference with its structure;
2. Dysregulation of the actin cytoskeleton;
3. Alteration of the glomerular basement membrane or its interactions with the podocyte;
4. Alteration of the negative surface charge of the podocyte.

Damage to podocytes triggers apoptosis and their detachment from the glomerular basement membrane. Further damage is triggered by cytokine release, mechanical stress, and loss of polarity, which ultimately leads to sclerosis and scarring of the glomerulus.

Various genetic mutations have been implicated in the pathogenesis of certain FSGS. In certain clinical variants, other mechanisms of injury, such as circulating factors (which cause recurrence of FSGS in transplanted kidneys), dysregulation of podocyte cell cycle resulting in immature podocytes (in collapsing variant), and role of parietal epithelial cell have been implicated.

As podocyte loss progresses, there is relative exposure of underlying basement membrane to parietal epithelial cells. The maladaptive interactions that follow lead to expansion of synechiae and leak of proteins into Bowman's space, ultimately leading to deposition of collagen and resultant sclerosis.

FSGS is known to progress to end stage kidney disease. Progression of the disease is enhanced by various cytokines and tubulointerstitial injury. The overexpression of transforming growth factor β (TGFβ) or its effector proteins secondary to activation of the renin-angiotensin system, the SMADS, other angiogenic factors, such as platelet-derived growth factor (PDGF), and VEGF have been implicated in this progression.

Mechanical stress further aggravates the injury. There is increased filtration due to defects in filtration barrier, which leads to hypertrophy of glomeruli. Resultant mismatch between glomerular basement membrane and decreased podocytes leads to further injury.

Clinical Features

The degree of proteinuria in FSGS can vary from nonnephrotic range to massive proteinuria along with other clinical features of nephrotic syndrome. About half of the patients may have hematuria, whereas 30 percent patients may have renal insufficiency. While hypertension is not a common feature in children with FSGS, it is common in adults.

Treatment of FSGS

Treatment of secondary forms is directed at the underlying disease, while in primary FSGS, immunosuppressive treatment is tried and is aimed at controlling proteinuria and preserving renal function.

Corticosteroids

Corticosteroids are the main component of immunosuppressive regimens either alone or in combination with other immunosupressants.

Oral corticosteroids remain the first line of therapy in children. They are used in the dosage of 60 mg/m^2/day up to 80 mg/day for four weeks followed by 40 mg/m^2/day up to 60 mg/day in divided doses for three consecutive days of a week for next four weeks and then tapered off for four more weeks. However, owing to the poor response to oral steroids in FSGS, high-dose intravenous methylprednisolone is used in certain protocols. In others, steroids are given in combination with other immunosuppressive drugs, such as alkylating agents or calcineurin inhibitors.

Though a calcineurin inhibitor, cyclosporin A is very effective in inducing remission; there are concerns about its long-term use. While in children with minimal change disease, cyclosporin A is reported to be safe even when used for more than five years; but in children with FSGS, there have been reports of chronic cyclosporin-induced nephropathy . The risk is higher in children younger than 5 years or when the drug is used for more than 36 months. Other concerns regarding cyclosporin use are about relapse on withdrawal of the drug and of secondary resistance. CsA acts by various mechanisms. It acts on T-helper cells to inhibit interleukin-2 (IL-2) production, cytotoxic T-cell proliferation, and activation of B-cell responses by helper T-cells. It also induces vasoconstriction of the glomerular afferent arteriole and interferes with glomerular basement membrane permselectivity to proteins. Another calcineurin inhibitor that can be used is tacrolimus.

Alkylating agents, such as cyclophosphamide or chlorambucil, could also be used for treatment of FSGS; however, they are usually not the drugs of choice, owing to their potential for bone marrow toxicity and neoplastic potential. Mycophenolate mofetil is a newer drug, which is showing a good response in nephrotic syndrome especially as a steroid-sparing drug.

The incidence of recurrence of nephrotic syndrome associated with FSGS is about 30 percent, despite the introduction of newer and more potent immunosuppressive regimens. Various therapeutic regimens, including preoperative plasmapheresis (PP), high-dose cyclosporine, IV cyclosporine, and adjunctive cyclophosphamide, have proven to be effective in preventing recurrence in transplanted kidney.

Membranous Nephropathy

MN is the most common cause of nephrotic syndrome in adults. It is rare in children. It can occur as an idiopathic variety or secondary to other disorders, such as autoimmune diseases, infections, and malignancies. It is characterized histologically by the uniform thickening of the glomerular capillary wall on light microscopy. On immunofluorescence, this thickening is associated with subepithelial granular immune complex deposits of immunoglobulin (Ig) G and as electron-dense deposits on electron microscopy. Ultrastructurally, the disease is classified into four stages based on the extent of deposition of these electron dense deposits.

Pathogenesis and Pathophysiology of Membranous Nephropathies (Addition by the Editor)

The glomerular 1gG deposits were initially believed to represent an accumulation of immune complexes arising from the circulation, as is found with glomerulonephritis in a rabbit model (chronic serum sickness). Other investigators have demonstrated that a circulating antibody reacted with and bound to the primary antigenic target located on prodocytes, indicating that the disease was caused by the in situ formation of immune complexes. More recently, M-type phospholipase A_2 receptor (PLA$_2$R) has been identified to circulate and bind to a conformational epitope (or epitopes) present on PLA$_2$R producing in situ deposits characteristic of those associated with membranous nephropathy. These autoantibodies are largely, but not exclusively, immunoglobulins of the 1gG4 subclass, similar to those seen in most instances of idiopathic membranous nephropathy in patients. There are preliminary data indicating an association between the clinical features (proteinuria and the nephrotic syndrome) and the presence and titer of PLA$_2$R autoantibodies.

Post-transplantation Membranous Glomerulopathy

Idiopathic MN recurs in 10 to 30 percent of patients 10 to 24 months after kidney transplantation de novo membranous glomerulopathy can also occur in 2 to 9 percent allografts after about 24 to 36 months post-transplant, which is the most common de novo glomerulopathy in renal allografts.

Clinical Features

The patient may present with either nephrotic range or nonnephrotic range proteinuria. Some patients may have associated hematuria. Hypertension may occur. Half of the patients undergo spontaneous remission of proteinuria. Variable degree of renal insufficiency is common, but ESRD occurs in small number of patients.

A patient with biopsy-proven membranous nephropathy is presented here (contributed by the editor) to illustrate extraordinarily high proteinuria and thromboembolic phenomenon. A 75-year white male had several hospital admissions for treatment of generalized edema (anasarca) between 2009 and 2010. Prior to December 2009, he was treated for recurrent pulmonary embolism with Greenfield filter and later placed on coumadin therapy. No source of deep venous thrombosis was identified. He had history of diabetes. In January 2010, he had a hospital admission for a percutaneous kidney biopsy. As of January 4, 2010, a random serum chemistry showed glucose 98 mg/dL (5.4 mmol/L), BUN 23 mg/day, creatinine 1.7 mg/dL, eGFR 42.7 ml/min; normal electrolytes; serum albumin 2.3 g/dL, and hemoglobin 11.4 g/dL. His 2-hour postprandial glucose was 125 mg/dL (6.9 mmol/L). He was treated with metformin 500 mg/day for diabetes which was initially considered to be the cause of his massive proteinuria. He had two percutaneous kidney biopsies; first one consisted of medulla but the second one showed cortex. He had had several 24-hour urinary studies for protein and creatinine clearance (Table 5).

Based on extraordinarily heavy proteinuria on January 11, 2010, prednisone 30 mg twice daily and mycophenolate mofetil (Cellcept®) 500 mg twice daily were initiated. Second kidney biopsy showed on light microscopy global glomerular basement membrane thickening (Fig. 1). Glomerular basement membrane "spikes" as seen on a silver stain were not well developed in this case. However, glomeruli show segmented margination of leukocytes, a feature suggestive of renal vein thrombosis (Fig. 2). Immunofluorescence study revealed glomerular basement membrane staining for IgG, C_3, C1Q, and Kappa and Lambda light chains (Figs 3 and 4). Electron microscopy confirmed stage 2 membranous glomerulonephritis (Figs 5 and 6).

After a week of treatment with corticosteroids, his 24-hour proteinuria (January 18 to 19) was decreased to 77949 mg. His renal function improved a bit. Serum creatinine decreased to 1.5 mg/dL with increase of eGFR to 52.3 ml/min. His hemoglobin increased to 12.9. He continued to take prednisone. Mycophenolate mofetil was discontinued. Instead he was placed on cyclophosphamide 50 mg po twice daily. He was admitted for the last time on March 25, 2010, for unremitting abdominal pain. A 24-hour urinary protein was 28863 mg with a creatinine clearance of 25.6 ml/min. He underwent exploratory laparotomy and rapidly deteriorated since then. The family requested to stop laboratory studies and therapies as of March 27, 2010. He died shortly thereafter.

Comments

Here was a patient with biopsy proven membranous nephropathy. Membranous nephropathy was considered idiopathic because no cause was found for secondary membranous nephropathy. He was hepatitis or lupus negative. Malignancy was thought but no source found.

Table 5. RGM 75-year white male: Serial 24-hour urinary studies for protein and creatinine clearance

Date	*Proteinuria*	*Creatinine Clearance*
2009 - 2010	mg/24 hour	ml/min
November 24	12163	55.7
December 12	24822	51.4
December 28	32269	87.2
January 11	82961	44.5
Prednisone and mycophenolate mofetil started.		
January 18	77949	ND/eGFR 52.3
Mycophenolate was replaced by cyclophosphamide, prednisone continued.		
March 20	8299	45
	Surgery done	
March 25	28863	25.6
Therapy withdrawn by family.		

ND = Not Done.

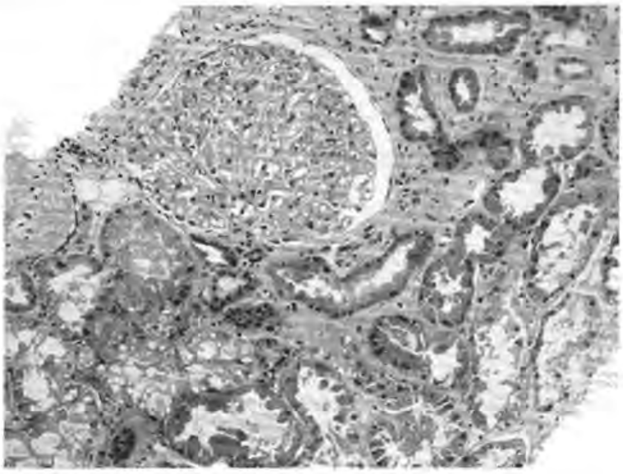

Figure 1: A hematoxylin and eosin-stained section reveals thickened glomerular capillary loops. There is focal mild interstitial fibrosis. (H&E, 20x objective) (*For color version, refer to plate 3*)

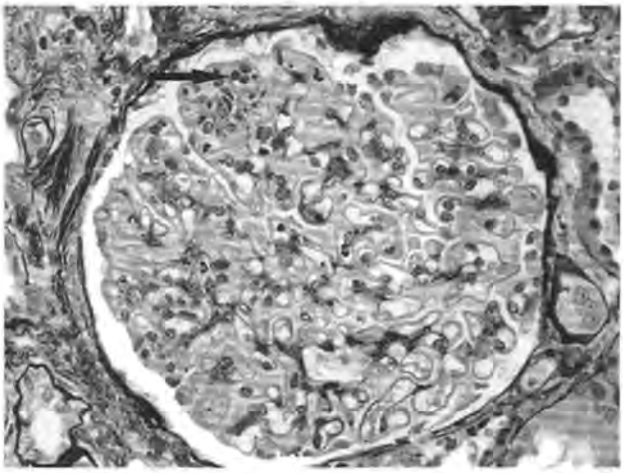

Figure 2: Glomeruli show segmental margination of leukocytes (arrow), a feature that is suggestive of renal vein thrombosis. Gomerular basement membrane "spikes" as seen on a silver stain are not well developed in this case. (Jones-methenamine silver, 60x objective) (*For color version, refer to plate 3*)

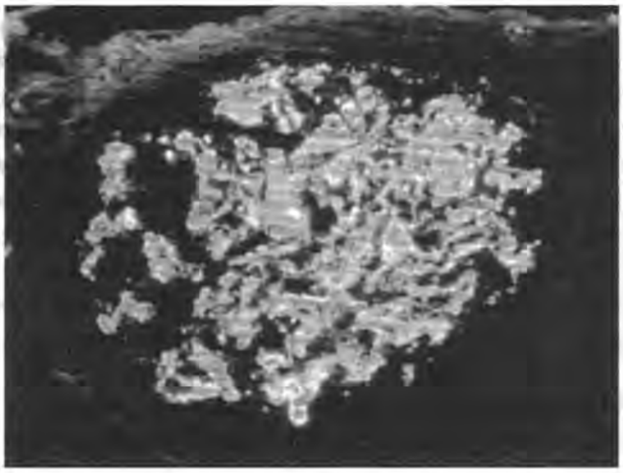

Figure 3: Glomeruli show global granular glomerular basement membrane staining for IgG. (Immunofluorescence, 40 x objective) (*For color version, refer to plate 3*)

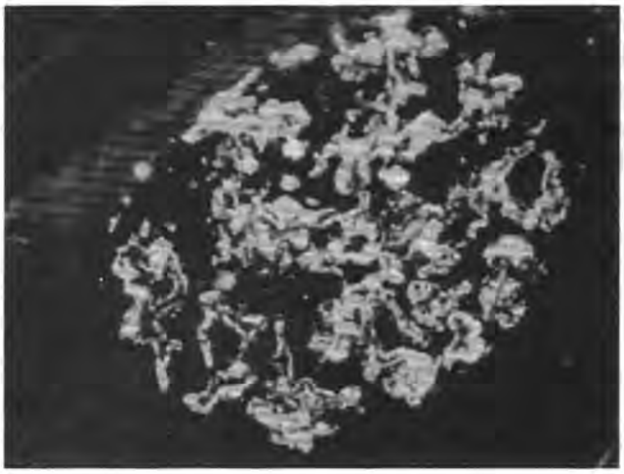

Figure 4: Glomeruli show global granular glomerular basement membrane staining for C3. (Immunofluorescence, 40x objective) (*For color version, refer to plate 3*)

He was taking no medication which may contribute to MN. He responded to therapy with corticosteroid and cyclophosphamide with remarkable decrease of proteinuria from 82 g to 28 g in a period of three months. His renal function was reasonably well preserved for the duration despite humongous proteinuria which was never reported in the literature. He died from postoperative complications which could not be treated adequately because of the wish of the family not to treat.

Treatment

The treatment is based on assessing the prognostic factors at illness onset and trying to achieve a balance between the risk of renal failure versus the risks of immunosuppression. Accordingly, patient is given either nonimmunosuppressive treatment, such as ACEI/ARB (see Editor's comment) or immunosuppressive treatment. The various medications used for immunosuppressive treatment are corticosteroids, alkylating agents, or

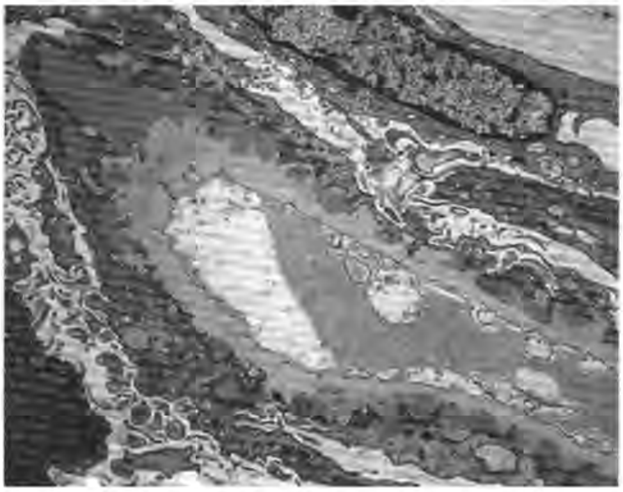

Figure 5: By electron microscopy, a glomerular capillary loop shows numerous subepithelial electron dense deposits with incorporation into the basement membrane. There is diffuse podocyte foot process effacement. (Electron microscopy, x 7400)

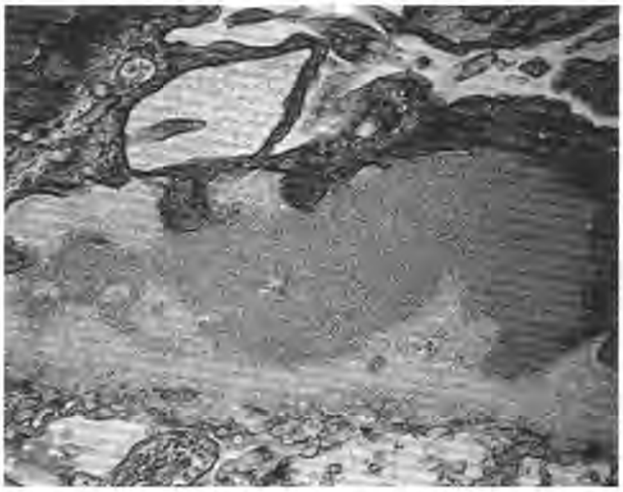

Figure 6: On higher magnification, the electron dense deposits do not show substructure. (Electron microscopy, x 33,000) Case courtesy of Dr LD Cornell, Mayor Clinic, Rochester, Minnesota, USA

calcineurin inhibitors. The role of steroids in membranous glomerulopathy is debatable, so is its dosage and duration of therapy. Editor feels that if general condition of the patient is stable in particular, without thromboembolic phenomenon requiring warfarin, it is reasonable to try a course of corticosteroid and cyclophosphamide to induce remission of proteinuria and yet preserve renal function. In post-transplant MN effects of anti-CD 20 antibodies (rituximab) were assessed. After 24 months of treatment with Rituximab in 5 patients with recurrent MN and proteinuria >3000 mg/day, serum creatinine decreased from 1.68 mg/dL to 1.42 mg/dL with corresponding increase of eGFR from 39.8 to 52.2 ml/min. (Addition by the Editor).

Ponticelli Regimen

This regimen is efficient in achieving remission in patients with membranous nephropathy. It consists of six months course of pulse methylprednisolone and chlorambucil. Other agents used in this disorder are cyclosporin A and mycophenolate mofetil.

Natural history or prognosis of untreated patients with idiopathic membranous nephropathy (Addition by the Editor.) In general, there is some consensus that treatment with corticosteroids without or with other immunosuppressive drugs such as cyclophosphamide has a definitive beneficial effects in altering the course of MN. A study from Italy in 1993 involving 100 biopsy-proven MN concluded that most patients with idiopathic MN maintain renal function for prolonged periods and are likely to have spontaneous remission. The above authors felt that their results do not support the use of glucocorticoids and immunosuppressive drugs in patients with idiopathic MN. Even an older study from Rochester, Minnesota, USA found no differences in the outcomes of renal function and protein excretion between untreated and treated patients.

Membranoproliferative Glomerulonephritis: Mesangiocapillary Glomerulonephritis

This is one of the least common types of glomerular diseases. Membranoproliferative glomerulonephritis (MPGN) can occur as a primary (idiopathic) disorder or it can occur secondary to other systemic disorders, such as collagen vascular disorders, hepatitis B and C, HIV, neoplasms, sickle cell disease, etc. The most common form in children is idiopathic, whereas secondary causes dominate in adults.

Pathology

Pathologically, there is diffuse mesangial cell proliferation and the thickening of capillary walls due to subendothelial extension of the mesangium. There are three variants of MPGN.

- **Type I (classical MPGN)** is the most common variant. Histologically, there is diffuse global capillary wall thickening as a result of subendothelial deposits of immune complexes secondary to the activation of the classical complement pathway and endocapillary hypercellularity. Subepithelial electron-dense deposits resembling "humps" as seen in poststreptococcal glomerulonephritis can be seen here.
- **Type II MPGN (dense deposit disease)** is characterized by intramembranous dense deposits. This type is associated with a serum Ig, C3 nephritic factor (C3NeF), which stabilizes C3 convertase (C3bBb), which causes persistent activation of the alternative complement pathway.
- **Type III MPGN** is considered as morphologic variant of type I, which has the presence of additional subepithelial deposits.

Clinical Features

The natural history of MPGN is characterized by spontaneous fluctuations in the severity of the disease with a slowly progressive course ultimately leading to end stage renal disease over a period of 10 to 15 years in about 40 percent of patients. Type II MPGN is known to have worse prognosis. The patients of MPGN present with one of the following features:

1. Nephrotic syndrome
2. Acute nephritic syndrome
3. Asymptomatic proteinuria and hematuria detected on routine urinalysis
4. Recurrent episodes of gross hematuria

Hematuria is a common feature in children, whereas hypertension and renal insufficiency are seen commonly in adults. Most patients have anemia, which is out of proportion to the severity of renal dysfunction and is thought to be due to complement mediated hemolytic anemia. Recurrence of MPGN is seen to occur in renal transplant recipients.

Treatment

Some of the patients with type I MPGN will undergo a spontaneous remission. The treatment of remaining patients is aimed at treating the underlying disease. Recommended drug therapy includes either oral corticosteroids or other immunosupressants. There is no good therapy for type II disease.

Amyloidosis

Amyloidosis is caused by deposition of fibrillar material called amyloid in various tissues. Amyloid is composed of portions of precursor proteins. These proteins assume a secondary beta sheet structure. Amyloidosis affects various organs; kidney is the most common of them. Renal amyloidosis usually manifests with proteinuria, often in nephrotic range. In some patients, there is progressive decline in renal function. Hypertension is rare even in the presence of severe renal dysfunction. Cardiomegaly is common.

Treatment

Treatment is mostly palliative. The treatment is derived from those developed for multiple myeloma. These consist of various chemotherapeutic agents such as thalidomide, lenalidomide, bortezomib, anti TNF agents, and stem cell transplantation. Colchicine may be tried.

Diabetic Nephropathy

Diabetic nephropathy is one of the major microvascular complications of both type1 as well as type 2 diabetes mellitus and is a leading cause of morbidity and mortality worldwide. About half of the patients with diabetes mellitus develop microalbuminuria at some point: of them, about one third will progress to proteinuria and progressive renal insufficiency, another third will revert to normal, while the rest will continue to be microalbuminuric. The stages of diabetic nephropathy will be found in Table 6.

Pathophysiology

Intracellular hyperglycemia that develops in diabetes stimulates biochemical and hemodynamic pathways. The resultant activation of signaling molecules and growth factors contribute to tissue damage. This is further aggravated by the genetic influence and hypertension.

Concept of Oxidative Stress

Certain renal cells, such as mesangial cells in glomeruli, glomerular epithelial cells, and proximal tubular epithelial cells, are unable to reduce glucose uptake in the presence of hyperglycemia of diabetes. The resultant increased uptake of glucose leads to increased production of reactive oxygen species (ROS). When the production of ROS exceeds local antioxidant capacity,

Table 6. Stages of diabetic nephropathy

Stage	Description	Clinical/lab features
1	Early glomerular lesions	Proteinuria<30mg/day, GFR increased, reversible with diet control
2	Incipient diabetic nephropathy	Proteinuria—30–300mg/day, GFR increased but will decline with progression of proteinuria, endothelial dysfunction, associated with diabetic retinopathy, cardiovascular disease.
3	Overt diabetic nephropathy	Proteinuria>300mg/day, GFR-declines, associated with diabetic retinopathy, cardiovascular disease
4	End stage kidney disease	GFR<10 ml/min, full fledged end stage kidney disease

oxidative stress occurs. When this occurs, oxidation of important macromolecules, including proteins, lipids, carbohydrates, and DNA ensues. There are a number of enzymatic and nonenzymatic sources of ROS in the diabetic kidney, which include autooxidation of glucose (glycolysis), transition metal-catalyzed Fenton reactions, advanced glycation, sorbitol/polyol pathway flux, mitochondrial respiratory chain deficiencies, xanthine oxidase activity, peroxidases, nitric oxide synthase (NOS), and NAD(P)H oxidase. ROS include free radicals such as superoxide, hydroxyl, and peroxyl and nonradical species, such as hydrogen peroxide (H_2O_2) and hydrochlorous acid (HOCl).

Activation of Renin-Angiotensin-Aldosterone-System

The RAAS causes kidney damage through several mechanisms, such as systemic and glomerular hypertension, increased glomerular capillary permeability, and local inflammation within the kidneys via release of several chemokines and profibrotic cytokines ultimately leading to glomerular fibrosis.

WHO DEVELOPS RENAL DISEASE?

An unknown but strong genetic influence exists for diabetic renal disease. Duration of diabetes, poor glycemic control, and hypertension are the strongest risk factors for the microvascular complications.

Prevention of Diabetic Renal Complications

1. Good glycemic control: DCCT and UKPDS studies have shown conclusively that a tight glycemic control lowers the risk of microvascular complications.
2. Adequate blood pressure control: Adequate BP control reduces risk of diabetic complications. BP should be controlled to <130/80 mm Hg or <125/75 mm Hg, if proteinuria is present.
3. Cessation of smoking.

Early Detection of Diabetic Kidney Disease

Screening for kidney disease should begin at the time of diagnosis in type 2 DM; whereas in type 1 DM, it should begin after five years of the diagnosis. Once patient develops evidence of kidney disease, further evaluation should be based on measurements of GFR and estimation of proteinuria. Measurement of cystatin C concentration can be used as a surrogate marker for GFR. Urinary albumin levels can be assessed by timed collections, both overnight and 24-hour collections, and by spot urine tests used to measure albumin creatinine ratio (ACR).

Management of Diabetic Kidney Disease

CVD Risk Reduction

As diabetic kidney disease is known to be a major risk factor for cardiovascular mortality, CVD risk reduction must be considered for any patient with diabetic kidney disease. Hypertension, dyslipidemia, and hyperglycemia should be managed more aggressively on the basis of treatment goals recommended for patients at highest risk of CVD. Target blood pressure should be less than 130/80 mm Hg, low density lipoprotein cholesterol level of less than 100 mg/dL, and a target HbA1c level of less than 7.0 percent.

Slowing Progression of Diabetic Kidney Disease

Satisfactory glycemic control (2h-postprandial glucose level of less than 200 mg/dL or 11.1 mmol/L) is the key to prevention of progression of diabetic nephropathy. Renin angiotensin inhibitor drugs have no physiological basis in mitigating diabetic kidney disease except by lowering blood pressure.

Restriction of Protein Intake

There is no conclusive evidence to show that low-protein diet slows progression of diabetic kidney disease; however, some studies have shown the usefulness of this strategy. A meta-analysis of various trials showed that, when compared with consumption of a normal-protein diet, treatment with a low-protein diet was not associated with a significant improvement in kidney function as estimated by GFR. However, a significant decrease in proteinuria or albuminuria as well as reduction in HbA_1C was observed in the low-protein diet group. The risk of malnutrition and compliance to low-protein diet remains main concerns. The American Diabetic Association recommends that patients with diabetic kidney disease restrict their animal protein intake to less than 0.8 g/kg per day.

Smoking Cessation

As discussed above, smoking cessation will be useful in slowing further progression of renal dysfunction.

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Tuberculosis of the Kidney

Jai Prakash, Biplab Ghosh

INTRODUCTION

Tuberculosis (TB) is one of the oldest diseases known to affect humans for over 7000 years. TB remains the single greatest cause of death due to microbial invasion in the world. Robert Koch discovered the cause of TB in 1882. The pathogenesis of renal TB remained obscure until Medlar reviewed 100,000 serial sections of the kidneys from 30 patients in 1926. He described bilateral cortical lesions in almost all cases suggesting that the kidneys had become infected through the bloodstream at the time of the primary lung infection. Surgical intervention for genitourinary TB was introduced in 1870, when the first nephrectomy was performed for pyonephrosis. In the prechemotherapeutic era, one third of patients died within one year after diagnosis, and one half died within five years. This chapter will address following issues related to the TB of kidneys and urinary tract:

1. Etiological agent
2. Epidemiology
3. Pathogenesis
4. Pathology
5. Clinical Features
6. Diagnosis
7. Differential Diagnosis
8. Management

ETIOLOGIC AGENT

TB of kidney and urinary tract, like other forms of the disease, is caused by members of the *Mycobacterium tuberculosis* complex. Of the pathogenic species belonging to the *M. tuberculosis* complex, the most common and important agent of human disease is *M. tuberculosis*. But the bovine tubercle bacillus (*M. bovis*) occasionally can be responsible. Tuberculosis caused by *M. bovis* is now uncommon in developed nations accounting for fewer than 1 percent of all cases of tuberculosis. Environmental Mycobacteria (*M. avium*) occasionally cause human disease, particularly in immunosuppressed individuals, including renal transplant recipients. Renal tuberculosis caused by environmental Mycobacteria in nonimmunosuppressed individuals is exceedingly rare. The vaccine strain, Bacille Calmette-Guerin (BCG), also has been the cause of renal lesions as a complication of intravesical instillation of BCG for the treatment of superficial bladder cancer. *M. tuberculosis* is a rod-shaped, nonspore-forming, thin, aerobic bacterium measuring 0.5 by 3 micron and is often neutral on Gram's staining but has the propensity of acid-fastness. Acid fastness is due mainly to the organisms' high content of mycolic acids, long-chain cross-linked fatty acids, and other cell-wall lipids.

EPIDEMIOLOGY

Tuberculosis is on the rise worldwide. Significant progress, particularly in the developed countries, was being made in the control of TB. In the 1980s, the epidemiology of TB, both in developed countries like the USA and in the emerging countries of Asia, Africa and Latin America, underwent a catastrophic change. TB resurfaced with the advent of AIDS epidemic, further exacerbated by war, famine, homelessness, poverty, and large scale immigration of population associated with these conditions. More than five million new cases of tuberculosis (both pulmonary and extrapulmonary) were reported to the World Health Organization (WHO) in 2005; >90 percent of cases were reported from developing countries.

With increasing incidence of tuberculosis overall, there has been relatively high rate of extrapulmonary tuberculosis with emergence of drug resistance as well. Genitourinary tract disease accounts for approximately 20 percent of extrapulmonary infection. After lymphadenopathy, the most common form of nonpulmonary tuberculosis is genitourinary disease, accounting for 27 percent (range, 14 to 41 percent) of cases in several surveys. In the prechemotherapeutic era approximately 3 percent of unselected autopsy patients and 26 percent of those dying of tuberculosis had evidence of genitourinary tract tuberculosis at autopsy. In the early chemotherapeutic era (1952 to 1960), approximately 11 percent of patients dying of tuberculosis had genitourinary involvement at autopsy. At the present time, it is estimated that significant genitourinary disease will develop in approximately 4 to 8 percent of nonHIV infected individuals with pulmonary tuberculosis, if adequate therapy is not instituted. Traditionally genitourinary tuberculosis has been a disease of young to middle aged adults with a male to female ratio of approximately 5:3. Renal tuberculosis is due to hematological spread from pulmonary infection. Only 5 to 15 percent of persons infected with the tubercle bacillus ever become ill from this infection. Of this group, approximately 3 to 5 percent have manifestation of genitourinary tract disease. The rate of tubercular disease among HIV-infected tuberculin positive individuals is 4 to 26 times higher than that among comparable HIV-infected tuberculin negative individuals, and is approximately 200 to 800 times that of general American population.

PATHOGENESIS

The pathogenesis of TB reflects the balance of intrinsic mycobacterial virulence and the host immunologic response. The interaction of *M. tuberculosis* with the human host begins when droplet nuclei containing microorganisms from infectious patients are inhaled. Alveolar macrophages phagocytize the bacilli. Invasion of macrophages by mycobacteria results largely from binding of the bacterial cell wall with a variety of macrophage cell-surface molecules, including complement receptors, mannose receptor, immunoglobulin IgG Fcγ receptor, and type A scavenger receptors. Phagocytosis is enhanced by complement activation leading to opsonization of bacilli with C3 activation products such as C3b. A complex series of events is probably generated by the bacterial cell-wall glycolipid lipoarabinomannan (LAM). LAM inhibits the intracellular increase of Ca^{2+}. Thus the Ca^{2+}/calmodulin pathway (leading to phagosome-lysosome fusion) is impaired, and the bacilli may survive within the phagosome. The survival of *M. tuberculosis* within it seems to depend on reduced acidification due to lack of accumulation of vesicular H^+-ATPase. If the bacilli are successful in arresting phagosome maturation, then replication begins and the macrophage eventually ruptures and releases its bacillary contents. Unique cell wall structure confers virulence to tubercle bacilli. The initial stages of infection are usually asymptomatic. About two to four weeks after infection, two host responses to *M. tuberculosis* develop: a macrophage-activating CMI response and a tissue-damaging response. The *macrophage-activating response* is a T cell-mediated phenomenon resulting in the activation of macrophages that are capable of killing and digesting tubercle bacilli. The *tissue-damaging response* is the result of a delayed-type hypersensitivity (DTH) reaction to various bacillary antigens; it destroys unactivated macrophages that contain multiplying bacilli but also causes caseous necrosis of the involved tissues. Although both of these responses can inhibit mycobacterial growth, it is the balance between the two that determines the form of tuberculosis that will develop subsequently.

With the development of specific immunity and the accumulation of large numbers of activated macrophages at the site of the primary lesion, granulomatous lesions (tubercles) are formed. These lesions consist of accumulations of lymphocytes and activated macrophages that evolve toward epithelioid and giant cell morphologies. Initially, the tissue-damaging response can limit mycobacterial growth within macrophages. Although *M. tuberculosis* can survive, its growth is inhibited within this necrotic environment by low oxygen tension and low pH. At this point, some lesions may heal by fibrosis, with subsequent calcification, whereas inflammation and necrosis occur in other lesions. Progressive infection within the lymph node contaminates efferent lymph, and when sequential lymph node barriers fail, thoracic duct lymph delivers mycobacteria to the venous blood, seeding the pulmonary bed as well as extrapulmonary sites, such as the skeletal system, lymph nodes, and most frequently, the kidneys. Thus, limited hematogenous dissemination due to low grade bacillemia can occur early in the process of granuloma formation when the number of mycobacteria is small, and most organisms are found intracellularly within the macrophages comprising the granuloma. Small granulomas rapidly form at the metastatic foci because mycobacterial immunity is evolving or is already established at the time of dissemination. Although the bacilli may remain viable, the granulomas may remain clinically silent for decades. On the contrary, severe hematogenous dissemination commonly is responsible for miliary tuberculosis rather than limited extrapulmonary disease. In miliary tuberculosis, the systemic features of illness overshadow the asymptomatic renal involvement.

Local factors play a significant role in the evolution of clinically significant renal tuberculosis. The small silent renal granulomas resulting from silent hematogenous dissemination are typically found bilaterally in the renal cortex and arise from capillaries within and adjacent to glomeruli. A glomerular location is not surprising in view of their high rate of perfusion (increasing the likelihood of delivering a bacillus in the setting of sparse bacillemia) and their favorable oxygen tension. Such cortical granulomas usually remain dormant for decades. In some patients, however, bacillary proliferation within the glomerular capillary leads to capillary rupture and delivery of organisms into the proximal tubule. Thus, the live bacilli reach the loop of Henle and get entrapped where they tend to survive as well; possibly on account of impaired phagocytosis in the hypertonic environment. Granuloma thus develops in the medulla. Therefore, clinically significant renal TB is usually initially localized to the medulla. Such intraparenchymal granulomas may persist as mass lesions but commonly cavitate into the calyceal system. Despite bilateral hematogenous seeding of the kidneys, clinically significant disease is usually unilateral. Communication of the caseating granuloma with the collecting system usually is responsible for the spread of bacilli to the renal pelvis, ureters, bladder, and accessory genital organs such as epididymis, seminal vesicle and prostate. In addition to epithelial infection by a luminal mechanism, lymphatic spread to contiguous structures also occurs as does direct hematogenous seeding of pelvic genital organs with clinical sparing of the kidney. In addition to the direct parenchymal destruction associated with advanced renal lesions, the fibrosis that accompanies the granulomatous process within the collecting system, such as infundibular strictures and renal pelvic kinking, adds an obstructive mechanism that may contribute significantly to progressive renal dysfunction.

Nearly a century ago, Osler pointed out that the clinical entity tuberculosis is the net result of two pathologic processes: one—'caseation'—destructive and dangerous; and the other—'sclerosis'—conservative and healing. Perhaps in no other form of tuberculosis are both these processes so important in determining the clinical impact of the tubercle bacillus on an organ system as in genitourinary tuberculosis. On the one hand, particularly in the preantimicrobial era, progressive destruction and caseating necrosis of the kidney leading to "autonephrectomy" have long been recognized as possible results of tuberculous seeding of the kidney. However, ureteral and calyceal scarring as part of the healing process can result in obstructive uropathy and comparable loss of renal function.

PATHOLOGY

Tuberculosis may involve the kidney as part of generalized disseminated infection or as localized genitourinary disease. The morphology of the lesions depends on the site of infection, the virulence of the organism, and the immune status of the patient.

Gross

There are two major morphologic forms of renal TB: ulcerocavernous and miliary. In the early stages of ulcerocavernous form, the kidneys appear normal or show perinephritis. Yellowish nodules may be found on the outer surface. On cut section, granulomas and ulcers in renal pyramid or medullary cavities can be seen. Larger cavities filled with caseous material communicating with collecting system may also occur. Other gross findings include multiple ulcers in the infundibular region of the calyces, calyceal stenosis with caliectasis, ulcers or strictures of the ureters with hydronephrosis, pyonephrosis, subcapsular collection or perinephric abscess. The end-stage kidney is nonfunctional ("autonephrectomy") and destroyed by the combined necrotizing and obstructive processes. Calcification in advanced lesions is common and may be focal or generalized, which produces a "putty" or "cement" kidney. The bladder may show ulcers or be grossly fibrotic and contracted. The gross appearance of miliary TB is characteristic, with the cortex studded with yellowish white, hard, pin-head sized nodules that on microscopy show several coalescent granulomas with central caseation.

Microscopy

The caseating granuloma is the classic microscopic finding in essentially all forms of tuberculosis. Granulomas are characterized by the presence of macropghages with engulfed bacilli surrounded by epithelioid cells and Langerhan's giant cells. There is often a cuff of lymphocytes and plasma cells surrounding the lesion. Caseating necrosis is characterized by amorphous cheese like material replacing the normal architecture of tissue. Its presence generally implies that the lesion is active. Later this may calcify. This dystrophic calcification suggests activity rather than healing. Healing occurs by fibrosis and scarring. Most renal granulomas originate as vascular lesions in the cortex. Although glomerular lesions predominate, with foci within the capillary tuft, granulomas may develop within capillaries in relation to the convoluted or collecting tubules. Lesions within the collecting system per se are usually at the nadir of the loop of Henle or in the pyramidal collecting tubule, always draining a vascular granuloma, and presumably developing in response to ulceration and discharge of these lesions into the collecting system. Focal sparing of tubules, glomeruli, or both within the granulomas (skipped lesions) is characteristic of renal tuberculosis. The enlarging medullary abscess extends to the papilla and commonly produces papillary necrosis. Several pyramids may be involved individually with a variable extent of destruction or may coalesce to destroy the bulk of the renal parenchyma.

In immunosuppressed patients the granulomas may be less well-formed and organisms may be more readily demonstrated. Caseous necrosis is less frequently seen. When immunosuppression is severe, and in cases where the infective organism is an environmental mycobacterium, such as *M. avium intracellulare*, the lesions may be more diffuse and poorly formed than the usual miliary lesions and the granulomatous response consisting of histiocytic cells with abundant pale cytoplasm packed with organisms ('multibacillary histiocytosis'). Caseous necrosis is not a feature. In some patients with pulmonary or disseminated tuberculosis, there is evidence of renal failure without typical miliary involvement or localized genitourinary lesions. In these cases biopsy has shown interstitial nephritis, usually, but not always, with granulomata. Proliferative glomerulonephritis due to immune complex disease has been reported.

CLINICAL FEATURES

Tuberculosis of the urinary tract is easily overlooked. Many patients present with lower urinary tract symptoms typical of "conventional" bacterial cystitis. A high index of suspicion enables early diagnosis. Most patients are between 20 and 40 years of age, with a male to female ratio of 5:3. Urinary tract tuberculosis is notorious for its insidious mode of presentation, with approximately 20 percent of cases diagnosed unexpectedly at operation or autopsy. As many as 20 to 56 percent of patients with active urinary tract tuberculosis are detected on the basis of an abnormal urinalysis (persistent pyuria or hematuria) or culture negative urine. They may have constitutional symptoms of tuberculosis or symptoms referable to the urinary tract. In patients with persistent pyuria, conventional urine cultures do not yield any growth, and the urine is usually acidic, hence the term acid-sterile pyuria is used. Of the symptomatic patients, approximately 75 percent of patients with urinary tract tuberculosis present with symptoms suggesting urinary tract inflammation. Recurrent bouts of painless hematuria should alert the clinician to the possibility of urinary TB in addition to other diseases such as IgA nephropathy. It occurs as a result of bleeding from the ulcerative lesions, inflammation of the urothelium, or rupture of blood vessel in the vicinity of a cavity. Colicky pain may occur, owing to the passage of clots or stones, or acute obstruction and may be observed in fewer than 10 percent of patients. Severe pain localized to the kidneys is uncommon. Constitutional symptoms usually associated with tuberculosis such as fever, weight loss, night sweats, and anorexia are seen in fewer than 20 percent of patients with tuberculosis restricted to the urinary tract. Indeed, the presence of such constitutional symptoms should suggest the presence of active tuberculosis in other organs. One third of patients have an abnormal chest X-ray.

Tubulointerstitial nephritis of tubercular origin may present as dehydration because of a concentrating defect. Dehydration and hyponatremia with concomitant constitutional symptoms may favor Addison's disease in such cases. Renal tuberculosis may present with slowly progressive advanced renal failure with normal size kidneys without evidence of calcification or gross anatomical distortion. In such cases renal histology reveals interstitial infiltrates with chronic inflammatory cells and granulomas. Caseation and acid-fast bacilli may be identified in few such cases. Pyuria is seen in some of these cases, but not in others. However, tubercle bacillus was not found in urine of patients suffering from tuberculous interstitial nephritis. Renal function improves with antituberculous therapy. No firm link has been established between tuberculosis and glomerulonephritis, although there are a number of case reports indicating dense deposit disease and focal proliferative glomerulonephritis in patients with TB. Chronic tuberculosis sometimes leads to amyloidosis, which is an important cause of renal disease and renal failure in India. Long standing renal TB may result in mild tubular proteinuria (<1 g/24 hours) in up to 50 percent of patients. About 15 percent excrete more than 1 gm of protein per day and some patients may develop nephrotic syndrome due to amyloidosis. Anemia is seen in less than 20 percent of patients with nonmiliary disease, but the frequency is higher in those with renal dysfunction. A few patients develop nephrogenic diabetes insipidus and others renal tubular acidosis. Hyporeninemic hypoaldosteronism may potentially result from the tubulointerstitial injury secondary to obstructive uropathy. Renal function is usually normal but renal insufficiency may occur if both kidneys are extensively damaged.

Tuberculosis, although an uncommon cause of progressive renal failure, but is an important one because, unlike many renal conditions, it is potentially preventable and easily treatable. However, there is little information on the contribution of tuberculosis to the burden of End Stage Renal Disease (ESRD). This is because of the fact that, whereas most of the world's tuberculosis is in developing countries, registries of patients with end-stage renal failure are mainly in the developed world. From published data on primary renal diagnosis (as a cause of chronic renal failure) from the United States, Europe, and Australasia, it is clear that tuberculosis is more common in Europe as a primary renal diagnosis (0.7 percent) than in either the United States (0.004 percent) or Australasia (0.16 percent). Data from the European Dialysis and Transplant Association (EDTA) registry in 1991 revealed that 195 of 30,064 new patients (0.65 percent) had renal failure caused by renal tuberculosis. There are three other major complications of renal tuberculosis: hypertension, superinfection with conventional bacteria, and nephrolithiasis. Renal vein renin sampling may be useful in predicting the outcome of surgery for patients with hypertension and renal tuberculosis. Nephrolithiasis has been reported in 7 to 18 percent of patients with renal tuberculosis, and superinfection has been reported in 12 to 50 percent of patients with urinary tract tuberculosis.

Hypercalcemia can occur in genitourinary and disseminated tuberculosis as a result of increased synthesis of calcitriol [1,25-$(OH)_2D_3$] by activated macrophages within the granulomas. Tuberculosis is more common in patients with renal failure than in the general population. There is evidence for a state of relative immunological anergy in uremia—as indicated by skin testing—but the incidence of tuberculin anergy is difficult to assess unless data on tuberculin reactivity before the onset of renal failure is available. Tuberculosis is a problem in hemodialysis patients, in whom it often presents as an insidious manner with anorexia, low-grade fever and weight loss. In some reports the majority of cases had extrapulmonary or, occasionally, military tuberculosis. It is mostly because of reactivation of quiescent disease. Though there are fewer reports of tuberculosis among patients undergoing CAPD (continuous ambulatory peritoneal dialysis), there is no reason why reactivation of tuberculosis is less likely in these patients. The clinical manifestations of renal tuberculosis are listed in Table 1.

DIAGNOSIS

Because of the nonspecific clinical feature of urinary tract TB, a high index of suspicion is necessary to diagnose genitourinary TB. By far the most useful screening test is urinalysis. Essentially, every patient with established urinary tract TB has an abnormal urinalysis with pyuria,

Table 1. Nephrological manifestation of renal tuberculosis (TB)

	Clinical feature	*Possible mechanisms*
*1.	Acute renal failure	Acute interstitial nephritis, obstructive uropathy
*2.	Chronic renal failure	Chronic interstitial nephritis, hydronephrosis, calcified kidneys, amyloidosis
**3.	Proteinuria and Nephrotic syndrome	Focal segmental sclerosis, amyloidosis, Proliferative Glomerulonephritis
4.	Dehydration, salt losing nephropathy	Renal Tubular Defect
5.	Hypertension	Aortoarteritis, renal artery aneurysm
6.	Hypercalcemia	Increased synthesis of calcitriol by activated macrophages within the granulomas
7.	Nephrolithiasis and superadded bacterial urinary tract infection	Suppressed immunity?

Urological manifestations like hematuria, pyuria, hydronephrosis, pyonephrosis, stricture of ureter and contracted urinary bladder are the common manifestations of classical renal tuberculosis.

*Renal tuberculosis is the rare cause of acute renal failure (ARF) or chronic renal failure (CRF).

**Tuberculosis is an important cause of nephrotic syndrome related to amyloidosis in India.

hematuria or both. The only exception is a patient with miliary dissemination in whom urinary tract seeding is a relatively recent and perhaps insignificant event. The asymptomatic patient with sterile-acidic pyuria must be considered as having TB until proved otherwise. The next step in the evaluation of such patients is the intermediate strength (5 TU) tuberculin test. Virtually every patient with urinary tract TB who is not receiving systemic steroids or who has not been rendered anergic by such debilitating conditions as advanced malignancy or HIV infection has a positive tuberculin test. Approximately two-thirds of the patients with urinary tract TB have evidence of old or current TB on chest roentgenography. The isolation of *M. tuberculosis* by urine culture is the definitive diagnostic test in renal tuberculosis.

Bacteriological Diagnosis

Urinalysis and Microscopy of AFB

Ideally early morning midstream urine specimens are collected over three to five successive days, because bacilluria is of low rate and intermittent. The most suitable containers are sterile 28-ml glass or plastic screw-capped bottles (Universal Containers). Specimens should be delivered to the laboratory as quickly as possible to prevent replication of bacterial and fungal contaminants. When delays are unavoidable, the urine samples should be refrigerated but not frozen. Samples are concentrated by centrifugation and deposits are examined microscopically after staining by the Ziehl-Neelsen or similar acid-fast techniques. Definitive diagnosis depends on the isolation and identification of *M. tuberculosis.*

Urinary Culture

Because most species of mycobacteria, including *M. tuberculosis*, grow slowly, four to eight weeks may be required before growth is detected. The transparent Agar medium facilitates early visualization of microcolonies by approximately one week. The development of commercial broth based systems for mycobacterial growth detection has permitted the automation of the diagnostic process. For example, systems such as the BACTEC 460, mycobacterial growth indication tube (MGIT) system, ESP (Extra Sensing Power) Myco-ESP culture system II, and BacT/ALERT MB susceptibility kit use Middlebrook 7H12 media with added material for detection of mycobacteria (radiometric and colorimetric systems). With these systems, mycobacterial growth can be detected in one to three weeks. Other rapid diagnostic techniques include high performance liquid chromatography to identify the spectrum of mycolic acids in the bacterial cell (which is useful after 7 to 10 days of culture), ELISA technique to detect mycobacterial protein antigens, and the detection of tuberculostearic acid by gas chromatography and mass spectroscopy.

Serologic Diagnosis

A number of serologic tests based on detection of antibodies to a variety of mycobacterial antigens are marketed in developing countries but not in the United States. Serologic tests using the soluble antigen fluorescent antibody (SAFA) test, a sandwitch adaptation of the solid-phase antibody competition test (SACT-SE), and the polymerase chain reaction (PCR) can be used for early diagnosis of TB.

IMAGING

There are a number of reviews covering the different procedures for the diagnostic imaging of genitourinary TB. The imaging includes plain radiography of abdomen, chest and spine.

Plain Radiographs

Plain radiographs of the chest and spine show evidence of old or active pulmonary or spinal disease in 50 to 70 percent of patients. In addition, plain radiographs of the urinary tract are important because they show calcification in the kidneys and in the lower genitourinary tract. Renal tuberculosis may be unilateral or bilateral. Calcification is seen in about 30 percent of cases. It may have a variety of patterns—punctate, speckled, or hazy. In advanced tuberculosis the whole pelvicalyceal system and ureter may be outlined by calcification—the so-called tuberculous autonephrectomy. Extensive dystrophic calcification in the kidney in some cases of advanced renal TB is described as "cumulus cloud" calcification.

Intravenous Urography (IVU)

Abnormalities in the excretory urogram may be seen in 70 to 90 percent of patients. High-dose IVU has traditionally been the gold standard tool to diagnose and evaluate genitourinary TB. It is still used in private practice but in many institutions it has been replaced by CT scan. Early tuberculosis is seen as irregularity of the papillary margins with reduced density of contrast medium in the affected areas. When lesions affect the calyceal infundibula there is no calyceal filling at urography and the infundibulum shows a typical 'pinched-off' appearance. The renal pelvis, which may be dilated initially, may eventually be obliterated, leading to a distorted appearance, called "hiked up" pelvis (Kerr Kink Sign). Ureteral disease initially presents as mucosal irregularity, together with diffuse dilatation or narrowing due to inflammation or edema. There may be single focus or multiple areas of ureteral involvement. Irregularities or multiple strictures lead to beading, so cork-screw appearance of ureter or hydroureter may be seen. Later thickening and straightening of the whole ureter may occur ("Pipestem" ureter), due to intramural fibrosis. Ureterovesical junction involvement may produce a stricture responsible for ureteral obstruction and patulous, rigidly dilated orifice associated with vesicoureteral reflux. The urinary bladder becomes fibrosed and small in more advanced disease (Thimble bladder).

CT Scan

It is the most sensitive investigation for identifying renal calcification and cavitary lesions, which occur in more than half of the cases of renal TB. In a retrospective study of 53 patients with the diagnosis of genitourinary TB, the most common findings on CT were parenchymal scarring (79 percent), hydrocalycosis, hydronephrosis or hydroureter (67 percent), and thickening of the walls of the renal pelvis, ureters, or bladder (61 percent). These findings are not specific and therefore, as with IVU, one must look for multiple abnormalities and consider them in conjunction with the patient's history and presentation.

DIFFERENTIAL DIAGNOSIS

Tuberculosis mimicks numerous diseases both clinically and radiologically. Chronic nonspecific urinary infections may be confused with renal TB. This is confounded by the findings that in about 20 percent of patients with renal TB, secondary bacterial infection may occur. Absence of response to usual antibiotics and presence of sterile pyuria should arouse suspicion of urinary TB, which must be excluded in patients with these findings. However, there are many other causes of sterile pyuria such as infection with *Chlamydia trachomatis*, mycoplasma, and ureaplasma, invasive fungal infection, chemical cystitis, and interstitial nephritis. Conditions causing recurrent painless hematuria, such as IgA nephropathy, bilharziasis, are often misdiagnosed as TB in endemic areas. In interstitial cystitis, lower urinary tract symptoms, similar to tuberculous cystitis may occur, but the urinalysis does not show gross pyuria and cultures for AFB are negative. Radiologically, chronic pyelonephritis, renal papillary necrosis, medullary sponge kidney, calyceal diverticulum, renal carcinoma, xanthogranulomatous pyelonephritis and multiple small renal calculi have to be differentiated from TB.

Of late, a few case of pseudotuberculous pyelonephritis have been reported in which caseating granulomas resembling TB were observed in the renal parenchyma but no mycobacteria were detected in the renal tissue or urine culture. The overall prognosis of TB of the urinary tract depends on the host resistance and the load and virulence of the organism. In many cases, foci in the urinary tract remain dormant indefinitely. Progression occurs through formation of tubercular granuloma, caseation, ulceration and dystrophic calcification. Most manifestations result from the complications, which can be prevented by timely chemotherapy and appropriate surgical intervention when indicated. With the advent of effective chemotherapy, the long-term complication and adverse sequelae of TB have been decreased significantly.

MANAGEMENT

The advent of effective chemotherapy has revolutionized the clinical management of urinary tract tuberculosis, although the recent increase in drug-resistant infection, amplified by the AIDS epidemic, threatens this success. Whereas in the prechemotherapeutic era extirpative surgery was the only hope of controlling infection, today medical cure is the rule. There is a continuing need for surgical intervention, but now it is for the correction of anatomic abnormalities caused by scarring rather than for the removal of infected tissues. The two goals in the management of urinary tract tuberculosis are: (1) the conservation of tissue structure and function (both with medical treatment and surgical relief of obstruction resulting from tuberculous scarring), and (2) antimycobacterial cure.

Chemotherapy of Urinary Tract Tuberculosis

The greatest milestone in the treatment of TB was the discovery of the antituberculous drugs, starting with streptomycin in 1944, followed by *para-aminosalicylic* acid in 1946, isoniazid (INH) in 1952, and rifampicin in 1966. The armamentarium was further strengthened by pyrazinamide, ethambutol, fluoroquinolone and so on. These discoveries were followed by the introduction of shorter courses of chemotherapy for all forms of tuberculosis. The chemotherapeutic approach to tuberculosis is based on the following general principles.

It is believed that there are three populations of organisms that must be considered when treating patients with active tuberculous infection. The largest number, and fortunately the most easily treated, are those that are extracellular. This group of organisms is actively multiplying and can be easily treated with two or more bactericidal drugs. A much smaller population of slowly or intermittently multiplying organisms is found at an acidic pH within macrophages (intracellular). Finally, there are a variable number of organisms exhibiting slow or intermittent multiplication at a neutral pH within closed caseous lesions. Curative therapy requires eradication of all three populations of organisms. Rifampin and rifabutin are the only drugs that are bactericidal for all three populations of *M. tuberculosis*. Isoniazid (INH) is bactericidal both for the actively growing organisms in cavities and for those slowly multiplying within macrophages. Streptomycin and the other injectable aminoglycosides are bactericidal only for the actively replicating extracellular organisms. Pyrazinamide is bactericidal only for intracellular organisms. The fluoroquinolones such as ciprofloxacin, ofloxacin, and levofloxacin are bactericidal for *M. tuberculosis* in vitro and achieve excellent concentrations intracellularly. All other drugs currently licensed for the treatment of tuberculosis are bacteriostatic. The primary role of bacteriostatic antituberculous drugs is to inhibit the development of mutants resistant to simultaneously administered bactericidal agents. Because of the increase in incidence of drug-resistant tuberculosis in recent years, it is now recommended that drug susceptibility testing be carried out on isolates from all patients, rather than just on isolates from the high-risk patient groups. Because the most common cause of the development of de novo drug resistance is failure of compliance by the patient, increasing attention is now directed to the use of directly observed therapy in which public health workers directly administer the therapy to the patient.

Modern short-course antituberculosis drug regimens are effective in all forms of tuberculosis. They are based on an initial two-months intensive phase of treatment in which, usually, four drugs—rifampicin, isoniazid, pyrazinamide, and ethambutol (or streptomycin)—are given, and they destroy almost all tubercle bacilli. This is followed by a four-month continuation phase in which only rifampicin and isoniazid are given, with the aim of eliminating the few remaining near-dormant, persisting bacilli. For success, all doses must be taken, and because a failure to comply with therapy is the major cause for treatment failure, the World Health Organization has stressed the importance of direct supervision of therapy. To render such observation easier for both patient and supervisor, the drugs may be given twice or thrice weekly during the continuation phase. Pyridoxine should be given with INH to prevent peripheral neuropathy. In situations in which the probability of drug resistance is high, fluoroquinolone may also be used until the result of drug susceptibility tests are available. Longer courses of antituberculous treatment ranging from nine months to two years are useful in patients who do not tolerate pyrazinamide, those responding slowly to a standard regimen, those with miliary or central nervous system (CNS) disease, children with multiple site involvement, and those with significant immunosuppression (e.g., AIDS, organ transplant recipients, etc.).

Treatment Regimens in Special Situations

Standardized treatment regimens have been derived for a number of special situations as given below.

HIV/AIDS

HIV-associated tuberculosis is managed similarly to that observed in the HIV-negative population with prolongation of therapy for an additional three to six months in those with AIDS. If the follow up culture is positive, prolonged therapy for up to two years may be needed based on the antibiotic sensitivity. Rifampicin is substituted with rifabutin in HIV positive patients who are receiving HAART to avoid drug interactions with rifampicin.

Treatment of Patients with Renal Failure

In patients with renal failure, isoniazide, rifampicin and pyrazinamide, which are eliminated by the biliary route, can be given in normal dosages. However, some advocate decreasing isoniazide dosage to 200 mg once daily in patients with advanced renal failure. Because streptomycin and ethambutol are excreted by the kidney, dosage modification of these drugs is necessary in renal failure. Streptomycin is administered at a dosage of 15 mg/kg every 24 to 72 hours for creatinine clearance less than 10 ml/min to maintain a therapeutic peak of 20 to 30 μg/ml. Monitoring for high pitched tinnitus, sense of fullness in the ears, and audiography may be useful. For ethambutol, 25 mg/kg should be given three times weekly if GFR is between 50 to 100 ml/min and twice weekly if between 30 to 50 ml/min. Monthly questioning for symptoms of visual dysfunction (alteration in visual field, acuity, and blue-green color vision) with early referral for ophthalmic examination may identify ethambutol toxicity with potential reversibility.

Treatment of Patients with Liver Disease

In chronic liver disease, isoniazid, rifampicin and one or more nonhepatotoxic drugs (streptomycin and ethambutol) can be used for 8 to 12 months. Pyrazinamide is contraindicated. In those with acute hepatitis unrelated to TB or its therapy, it is safer to defer the chemotherapy until the acute hepatitis has resolved. If immediate treatment of TB during acute hepatitis is mandatory, streptomycin plus ethambutol for a period of three months followed by isoniazide and rifampicin for six months may be advised.

Drug Resistant Disease

In recent years, there has been a worrisome increase in the incidence of multidrug-resistant tuberculosis, which, by definition, is caused by bacilli resistant to rifampicin and isoniazid, with or without resistance to other drugs. Therapy requires the use of at least four drugs that are selected, on the basis of drug susceptibility tests, from ethionamide, prothionamide, quinolones (e.g., ofloxacin), newer macrolides (e.g., clarithromycin), cycloserine, kanamycin, viomycin, capreomycin, thiacetazone, and para-amino-salicylic acid. These are less effective and often more toxic and/or costly than the first-line drugs. Duration of therapy is based on bacteriologic response but may be 18 mo or longer.

Two types of genitourinary tract tuberculosis are particularly difficult to treat—'the autonephrectomized' kidney destroyed by tuberculosis and now presenting as a nonfunctioning, avascular, calcified, caseous mass; and prostatic tuberculosis. In both these circumstances, delivery of antituberculous therapy to the site of infection is fraught with difficulty.

Monitoring of Patients

After two months of intensive chemotherapy, urine is cultured for *M. tuberculosis* for three consecutive days. If cultures are still positive, sensitivity is done and treatment modified accordingly. After completion of treatment, all patients should have three consecutive early morning samples of urine cultured for *M. tuberculosis*, and this is repeated after three months and one year. IVU is repeated at the end of two months and at the completion of treatment to detect any evidence of obstruction. In cases of renal calcification, the patient should be evaluated yearly by 3 morning urine samples for culture of Mycobacteria and plain X-ray abdomen for up to 10 years because calcification may harbor *M. tuberculosis* and may progress to destruction of kidney.

Surgical Management of Urinary Tract TB

In the prechemotherapeutic era, surgical ablation of infected foci was the only therapy available for renal TB. Without surgery, the 5-year survival rate for such patients was 15 to 42 percent, but with surgery, 10-year survival rates approached 50 percent. The current focus is on organ preservation and reconstruction as opposed to excision. Furthermore, when surgical intervention is mandated, it should be delayed until medical therapy has been administered for at least four to six weeks. Classically, the indications for nephrectomy were (1) a nonfunctioning kidney with or without calcification; (2) extensive disease involving the whole kidney, together with hypertension and ureteropelvic junction (UPJ) obstruction; and (3) coexisting renal carcinoma. Skutil and Obsitnik advocated nephrectomy for some patients with persistent tuberculous cystitis or those with secondary development of nephrolithiasis. The main indication of epididymectomy is a caseating abscess that is not responding to chemotherapy. Involvement of the testis is uncommon; therefore, orchiectomy is required in only 5 percent of cases. Relief of ureteric obstruction by stenting or percutaneous nephrostomy may aid functional recovery, especially in patients with good renal cortical thickness, limited renal involvement, and a GFR of more than 15 ml/min.

KEY POINTS

1. Tuberculosis is a common disease worldwide, but is relatively uncommon in developed nations.
2. Tuberculosis of the kidney is usually a part of generalized disseminated infection. Approximately two-thirds of the patients with urinary tract TB have evidence of old or current TB on chest X-ray.
3. The risk of acquiring the disease is increasing in immunocompromised individuals (HIV positive persons, patients on dialysis and kidney transplant recipients).
4. Clinical manifestations of renal tuberculosis involving excretory system of kidney: hydronephrosis, stricture, pyonephrosis, renal calcification, small bladder and distorted calcified kidney are much more common than renal parenchymal involvement: interstitial nephritis, glomerulonephritis or amyloidosis.
5. Renovascular hypertension and end-stage renal disease are the rare manifestations of renal tuberculosis.
6. High index of suspicion is required for the diagnosis of renal tuberculosis because the symptoms are nonspecific.
7. With the recent development of antitubercular drugs and particularly with the introduction of short course chemotherapy, prognosis for all forms of tuberculosis has markedly improved.

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SECTION 6

STONE DISEASE

- Urinary Stones

33

Urinary Stones

Anil K Agarwal, Christopher Valentine

Stones of the urinary tract account for 0.07 to 0.1 percent of all hospital admissions in the United States. The incidence of stones increases with age. Stones commonly present between 18 to 45 years of age and are more common in white race. Approximately 7 percent of males and 3 percent of females over age of 30 years have urinary stones; 12 percent of American males and 5 percent of American females will suffer from stones by age 70. Lifetime risk of stone formation is about 20 percent in white males, 5 to 10 percent in white females, 6 percent in African American males, and 2 percent in African American females. Asians and Hispanics have an intermediate risk.

Urinary stones are common worldwide, but the incidence of stones has increased in industrialized nations largely attributable to changes in dietary patterns, especially, increase in protein and salt intake. Increasing prevalence of obesity and metabolic syndrome has been found to be associated with higher incidence of uric acid stones, since the renal expression of insulin resistance may be a low urine pH and low urine ammonium, increasing the risk of uric acid precipitation. There may be geographic variation in the incidence and prevalence of stones. Annual age-adjusted incidence from 1950 to 1974 was estimated to be 103 and 33 per 100,000 in males and females, respectively, in Minnesota and 123 and 36 per 100,000, respectively, in North Carolina. Although a higher incidence of stones was found in hot and dry climate, no regional difference could be demonstrated when differences in sunlight, temperature and beverage consumption were adjusted.

Recurrence of stones is more common than is generally appreciated. First-time stone formers are likely to have a recurrence rate of 15 percent at 1 year, 35 to 40 percent at 5 years, and 50 percent at 10 years. Untreated, there is a lifetime recurrence risk of 80 percent. A higher rate of recurrence has been noted in referral centers (50 to 80 percent recurrence over five years), known as 'Stone clinic effect'. A higher relative risk of stone recurrence is noted in those with a positive family history (2.57 over eight years in Health Professional study of 38,000 men) and in those with a higher number of stones. Patients with low (<1L/day) urine volume have increased incidence of stone formation (15 percent).

PATHOPHYSIOLOGY OF STONE FORMATION

The stone formation begins with nucleation (particle formation), followed by aggregation and crystal growth depending upon saturation of urine with stone forming substances (i.e., calcium, oxalate, phosphorus, uric acid, cystine etc.). When present in normal concentration, these substances remain in dissolved form in normal urine. Product of the corresponding ions (for example product of calcium x oxalate) in this phase is referred to as solubility product. A further increase in the concentration of free ions leads to supersaturated, 'metastable' urine, where the crystallization can proceed and existing stones can grow. Continued increase in ion product will lead to 'unstable' urine with formation of new stone (formation product). The presence of a heterogeneous nucleus (e.g., a foreign body), or nanobacteria, can provide a nidus, which facilitates growth of stone. Some ions have a propensity to precipitate more readily in the presence of certain other ions (such as calcium and uric acid) a phenomenon called epitaxial growth. Once formed, crystals need to attach to urinary epithelium to grow and can do so on subepithelial papillary calcifications called Randall's plaque or an area of injured epithelium.

Even though it is common for an individual to have metastable urine during the course of the day, the stone forming ions (i.e., calcium, oxalate, phosphorus, uric acid, cystine, etc.) can remain in solution in normal urine, with stone formation in a minority of people. Normal urine contains inorganic and organic substances that are inhibitors of nucleation, crystallization and aggregation. This may be due to the absence of inorganic or organic substances that inhibit crystallization in normal urine. These agents can modify one or more phases of stone formation, i.e., nucleation, crystal growth and aggregation. Citrate, pyrophosphate and magnesium inhibit calcium phosphate stone formation. Calcium oxalate stone formation is inhibited by nephrocalcin, Tamm-Horsfall protein, glycosaminoglycans, and RNA fragments. The changes in pH of urine are important in inhibition or promotion of stone formation. Presence of urinary tract abnormalities predisposes to stasis and infection associated stones.

Staghorn calculi are branching stones that extend from one calyx to another. These are more likely to be composed of struvite, uric acid and cystine and require surgical intervention for removal. Nephrocalcinosis refers to the presence of calcification in renal parenchyma and can occur in primary hyperparathyroidism, medullary sponge kidney, distal renal tubular acidosis (RTA), milk alkali syndrome and Dent's disease.

Types of Stones

Stones can be composed of any substance that is present in sufficient quantity and concentration in urine. Calcium stones are the most common urinary tract stone, responsible for 75 percent of all urinary stones. The majority of the calcium stones are composed of calcium oxalate. Less common types of stones include infection-associated stones, uric acid stones, drug-induced stones and cystine stones (Table 1).

Calcium Stones

Various metabolic defects leading to stone formation are commonly detected by 24-hour urine studies in stone formers and predict increased risk of calcium stone formation and recurrence (Table 2). Systemic conditions that predispose to hypercalciuria, such as primary hyperparathyroidism and type 1 RTA are associated with calcium stones.

Table 1. Types of urinary stones

Type of Stone	*Frequency (%)*	*Risk Factors*
Calcium	75	
Oxalate	36-70	Hypercalciuria, hyperoxaluria, hyperuricosuria, hypocitraturia, hypomagnesuria, low urine volume
Phosphate (Brushite-$CaHPO_4 . 2H_2O$ Apatite- $Ca_5(PO_4)_3 . OH$)	6-20	Primary hyperparathyroidism, RTA, Milk alkali syndrome
Mixed	11-31	
Noncalcium		
$Mg\ NH_4\ PO_4 . 6H_2O$ (Struvite), and $Ca_{10}[PO_4]_6 . CO_3$ (Carbonate apatite)	6-20	UTI with urease producing bacteria, abnormal anatomy
Uric acid*	6-17	Gout, hyperuricosuria, chronic diarrhea, low urine pH
Cystine	0.5-3	Cystinuria
Miscellaneous	1-4	
Xanthine* and hypoxanthine*		Xanthinuria
Beta-2 microglobulin		Renal insufficiency, dialysis
2,8 dihydroxyadenine*		2,8 dihydroxyadeninuria
Matrix stones*		
Drug Induced		
Triamterene*, Indinavir*, Sulfa, Silicate*, Oxipurinol, ephedrine		Therapy with respective drug

* radiolucent stones

Table 2. Risk factors for calcium urolithiasis

Hypercalciuria - 60%		
Idiopathic	a. Absorptive	Increased 1,25 D level, increased vitamin D receptors, low PTH
	type I	High fasting and postprandial calcium excretion on restricted diet
	type II	High fasting, but normal postprandial calcium excretion on restricted diet
	b. Resorptive	Prolonged immobilization, osteolytic cancer, hyperthyroidism lead to increased mobilization of calcium, suppressing PTH; hyperparathyroidism also causes increased resorption
	c. Renal	Decreased tubular reabsorption of calcium, high PTH
	d. Unclassified defects	Various combinations of serum calcium and PTH
Secondary		Hyperparathyroidism, hypercalcemia, granulomatous diseases, vitamin D intoxication, glucocorticoid excess, thyrotoxicosis, immobilization, high dietary intake
Hyperuricosuria		High protein diet, therapy with probenecid, salicylates, ascorbic acid, obesity, gout, alcoholism, inborn errors of metabolism, hematologic malignancies
Hypocitraturia- 10-40%		Acidosis (RTA 1, acid-ash diet, chronic diarrhea, lactic acidosis, acetazolamide therapy), potassium depletion, high salt intake, chronic renal failure, UTI, idiopathic
Hyperoxaluria- 10-60%		
	Enteric hyperoxaluria	Crohn's disease, Celiac sprue, jejunoileal bypass, ileal resection, pancreatic insufficiency, biliary obstruction or resection, bacterial overgrowth, blind loop syndrome
	High dietary intake	
	Primary hyperoxaluria type 1 and 2	Genetic defect
	Miscellaneous	Pyridoxine deficiency, ethylene glycol toxicity

Population studies have suggested that dietary factors contributing to calcium stones include low fluid, high salt, and high animal protein intake. High sulfur content of animal protein is thought to result in increased production of sulfuric acid, which would buffer with bone and cause resorption of calcium and promote hypercalciuria. In contrast to previous thinking, low calcium intake in general population has been found to be associated with increased prevalence of stone disease. This is thought to be due to increased availability of free oxalate for absorption in the intestines, which leads to hyperoxaluria.

Genetic susceptibility to stone formation may be due to particular mutations, as in gene CLCN5 (Dent's disease) and in gene AGXT which alters tubular function. Other mutations may have a role, since there is a higher risk of recurrence of stones in those with a positive family history of stones.

Multiple, recurrent stones are uncommon (<5 percent) in the absence of risk factors. Some disease states are particularly likely to cause high stone load. Milk-alkali syndrome resulting from intake of calcium based antacids for the treatment of peptic ulcer disease used to be a common cause of stones. Production of vitamin D precursors by macrophages is associated with hypercalcemia, hypercalciuria and calcium stone formation in sarcoidosis. Gout and myeloproliferative disorders with high cell turnover and uric acid production are risk factors for uric acid or calcium stone formation. Malabsorption of fat, with saponification of calcium leads to excessive oxalate absorption and stone formation in Crohn's disease and jejunoileal bypass. Resorptive hypercalciuria and recurrent urinary tract infections during prolonged immobilization, paraplegia, and neurogenic bladder predispose to infection associated stones. Medullary sponge kidney is associated with bilateral stones.

Presentation of Urinary Stones

Stones are often detected incidentally in asymptomatic persons while undergoing imaging studies of abdomen for unrelated reasons (Fig. 1). Prolonged absence of symptoms is not uncommon, although presence of a higher number of stones is associated with an early onset of symptoms. Awareness of metabolic defects has resulted in referral of patients with a history of renal calculi for evaluation.

Flank pain is the most common presenting feature. The intensity and character of the pain vary, depending upon location of stone, and presence or absence of urinary tract obstruction. Stones in the renal pelvis without obstruction usually cause dull flank pain and, occasionally, tenderness. Smaller stones that tend to cause ureteric obstruction (Fig. 2) lead to severe, paroxysmal pain with waxing and waning with peristaltic movement of ureter. Severe pain is usually associated with nausea and vomiting, sometimes leading to dehydration. Ileus may be associated. As the stone traverses the urinary tract, the location and radiation of the pain change. The pain resolves with passage of the stone. Stones in the lower part of ureter may be associated with radiation of pain to testicle or labia on the same side. Pain due to stone in the trigone of the bladder may be referred to the tip of the urethra. Microscopic hematuria is present in over 90 percent of patients and dysuria may be associated. Occasionally, recurrent urinary tract infection may be the presenting symptom but, more often, the stones are caused by persistent infection with urea splitting bacteria. Renal dysfunction can occur if the obstruction is not relieved, infection is not treated or if there are invasive staghorn calculi (Fig. 3).

DIAGNOSIS

Clinical presentation of ureteric stone may be classic with severe, acute flank pain, hematuria and associated nausea and vomiting. A triad of flank pain, hematuria and positive KUB (Kidney, Ureter and Bladder) film (Fig. 4) is present in 90 percent of patients presenting with acute stone pain. Some degree of hematuria is present in most cases, but absence of blood does not exclude the diagnosis of urolithiasis. Obstruction of lower urinary tract with renal failure may be associated with a distended bladder on physical examination.

Various imaging techniques can be used to document the location and degree of obstruction caused by the stone (Table 3). While the decision to do a particular imaging study can be made based on characteristics of the individual presentation, the most effective technique is a noncontrast helical stone CT study. The CT scan may also be helpful in providing an alternative diagnosis. Ultra low dose CT scan with radiation dose equivalent

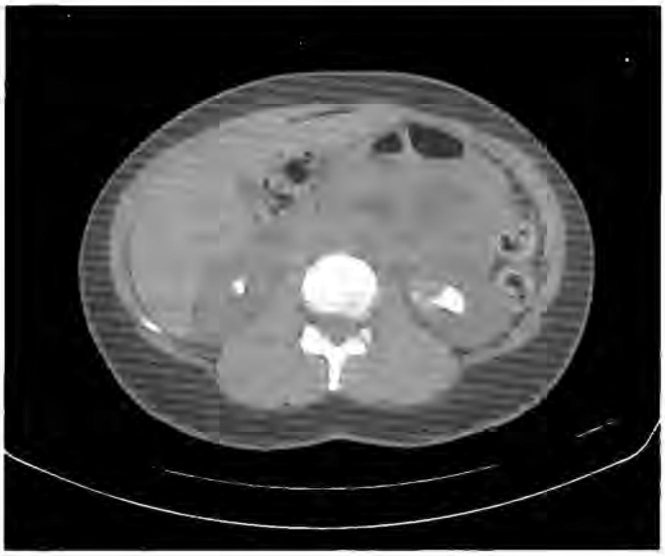

Figure 1: CT scan of the abdomen showing stones in medulla of both kidneys. The stone in left kidney is filling the pelvis and is a staghorn

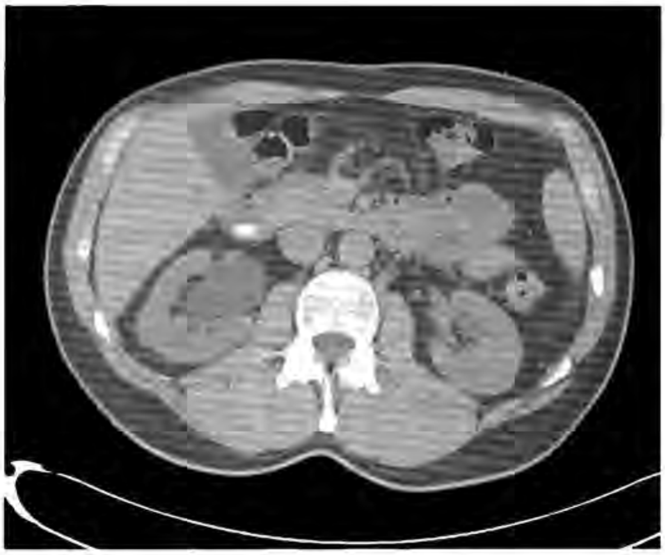

Figure 2: CT scan of abdomen is showing dilated right renal pelvis, signifying hydronephrosis of right kidney. There is a stone in the right ureter causing obstruction

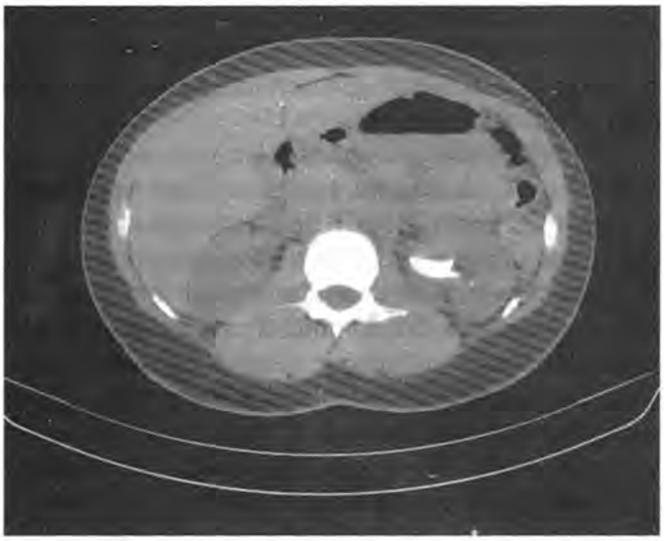

Figure 3: CT scan of abdomen showing staghorn calculus filling the pelvis of left kidney and branching into calyces

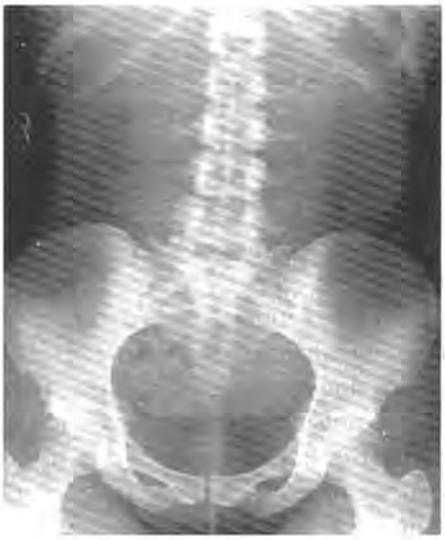

Figure 4: Plain radiograph of the abdomen (KUB film) showing radiopaque stone in right kidney

Table 3. Radiologic testing for stone disease

Modality	*Sensitivity*	*Merits*	*Disadvantages*
CT stone study (spiral CT)	95%, (95% specific)	Better than IVP in acute pain, no contrast, quick	Expensive, not universally available, X-ray exposure
IVP (Intravenous pyelography)	65%	Provides structural and functional data, detects radiolucent stones	More expensive, requires contrast administration
Ultrasound	10-25%	No X-ray exposure, noninvasive, accurately detects hydronephrosis, may use for follow-up and for pregnant patient	Operator dependent
KUB (Kidney, Ureter and Bladder) film	50-65%	Inexpensive, readily available, improves sensitivity and specificity of IVP. Should be done to differentiate radiopaque from radiolucent stones	Misses radiolucent and small stone
MRI		Better stone localization	Investigational, expensive, currently no established role

to that of KUB may be almost as good as a standard dose helical CT in diagnosis of renal and ureteral calculi.

Differential Diagnosis

The clinical presentation of ureteric colic is usually quite characteristic. However, common conditions causing acute abdominal pain should be excluded. Intestinal obstruction can cause severe colicky pain, is not associated with hematuria and has suggestive history. Acute appendicitis may be diagnosed with physical examination and CT scan. Diagnosis of disk protrusion requires CT or MRI scanning of spine. Ectopic pregnancy with lower abdominal pain can be diagnosed with pregnancy test. Clot colic from another cause of bleeding within the urinary tract (such as renal cell carcinoma) will result in obstruction but no evidence of calculus. Acute pyelonephritis is usually associated with fever, chills and bacteriuria. Renal artery dissection, acute nephritis and loin pain hematuria syndrome can mimic the pain due to stone disease. Dissection of aorta is a life-threatening emergency that can be diagnosed by physical examination and imaging studies.

MANAGEMENT

The management of ureteric colic includes hydration, analgesics and relief of obstruction (Fig. 5). Strong analgesics, narcotics or nonsteroidal anti-inflammatory drugs are usually required for pain relief. Caution should be taken not to prescribe NSAIDs in those with renal insufficiency. Stones smaller than 5 mm usually spontaneously pass. Stones 7 mm or larger are unlikely to pass without intervention. There is some evidence that use of long acting calcium channel blocker nifedipine and alpha-blockers, alone or in combination with steroids, may be helpful in expulsion of stones. Further management of a stone that fails to pass depends upon its size, characteristics and associated obstruction or infection, which will necessitate urologic intervention.

Urologic Interventions for Stone Unable to Pass Spontaneously

With currently available urologic techniques, 98 percent of all stones that are unlikely to pass spontaneously can be removed without resorting to open surgery. Management of difficult or multiple stones will require a combination of minimally invasive surgery and endourologic procedures. Urgent intervention with nephrostomy or stenting to relieve obstruction is needed if there is intractable pain, anatomical defect with nonpassage of stone, pregnancy, infection, obstruction or acute renal failure.

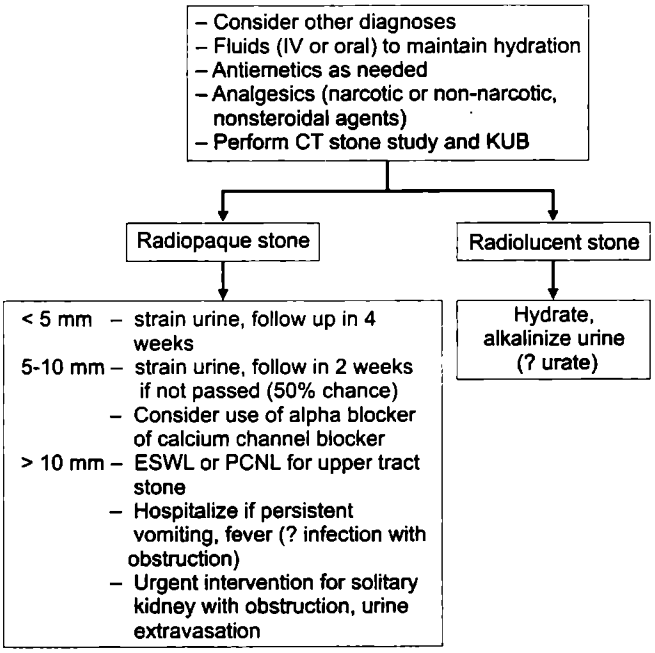
– Consider other diagnoses
– Fluids (IV or oral) to maintain hydration
– Antiemetics as needed
– Analgesics (narcotic or non-narcotic, nonsteroidal agents)
– Perform CT stone study and KUB
Radiopaque stone
Radiolucent stone
< 5 mm – strain urine, follow up in 4 weeks
5-10 mm – strain urine, follow in 2 weeks if not passed (50% chance)
– Consider use of alpha blocker of calcium channel blocker
> 10 mm – ESWL or PCNL for upper tract stone
– Hospitalize if persistent vomiting, fever (? infection with obstruction)
– Urgent intervention for solitary kidney with obstruction, urine extravasation
Hydrate, alkalinize urine (? urate)

Figure 5: Management of acute ureteric colic

Lithotripsy has evolved as the treatment of choice to facilitate stone removal. It is particularly more useful for smaller stones (<2.5 cm) and for stones in the renal pelvis and upper third of ureter. Extracorporeal shock wave lithotripsy (ESWL) is typically used, but significant enhancement of endoscopic lithotripsy with utilization of ultrasonic, electrohydraulic or laser probes has resulted in good results in difficult cases. Larger stone burden requires multiple sessions of lithotripsy. A combined approach with minimally invasive surgery such as lithotripsy followed by percutaneous nephrolithotomy (PCNL) or ureteroscopic removal of stones is often required.

Lithotripsy is generally well tolerated, but does require anesthesia and can be associated with complications. Skin bruising and ureteric colic from small fragments of stone are not uncommon. Urinary tract obstruction can occur in 2 to 3 percent of patients after single small stone treatment. Recurrent stone formation after lithotripsy may be a result of residual tiny fragments of the stone. Hematuria may result that may require radiologic intervention, such as embolization of the affected vessel. Perinephric hematoma and pancreatitits can result from direct injury. Perhaps related to nephron injury, new onset of hypertension (8 percent) and aggravation of pre-existing hypertension has been noted. Renal dysfunction could result, especially in those who undergo repeated lithotripsy and have small size kidneys. Due to the noninvasive nature of the procedure, there has been an increase in the intervention rate for small stones. Despite shorter hospital stay and lower cost as compared to surgery, the overall cost of stone management has increased with lithotripsy.

Lithotripsy is contraindicated in medical conditions involving close proximity of vital organs to the stone, and intolerance to radiation exposure. These conditions include pregnancy, aneurysm of renal artery or aorta, uncorrected bleeding disorder and severe uncontrolled hypertension. Patient should be able to tolerate anesthesia. Large stone-burden, grossly distended calyces, grossly abnormal anatomy (such as horseshoe kidney), ureteric stenosis distal to stone, and impaired mobility of ureter make the procedure ineffective, due to ineffective drainage of stone fragments.

Other techniques for stone retrieval include urologic procedures, such as transurethral ureterorenoscopy for stones in lower two-thirds of ureter that are not amenable to lithotripsy due to interference by pelvic bones. A Dormia basket or endoscopic lithotripsy can be used to remove the stone.

For stones larger than 2.5 cm, PCNL is the procedure of choice. It can also be used for most staghorns, and in the presence of anatomic abnormalities of the urinary tract. Cystine stones are hard in consistency and could be resistant to lithotripsy. These can be treated with PCNL. Hospital stay and recovery time are shorter as compared to open surgery. This can also be used for irrigation of renal pelvis to dissolve larger stones.

An open surgical procedure (nephrolithotomy) is rarely required, especially in those with normal urinary tract anatomy. This results in larger incision and longer hospital stay and recovery. Nephrectomy is an extreme measure, required in exceptional cases.

Medical Management of Stones

It is now well-recognized that the majority of stone formers have metabolic defects. Medical evaluation and prevention of stone disease by modification of these defects can result in a significant reduction in morbidity, loss of work and the financial burden of stone disease. While there is some debate as to whether one should evaluate a patient with a first stone, there is no doubt that recurrent stone formers should be thoroughly investigated. Even for the first time stone former, a limited approach is useful.

Limited Evaluation of First-Time Stone Former

The high recurrence rate of kidney stones (approximately 50 percent in males and 40 percent in females over 10 years of follow up) is the rationale behind the recommendations for limited evaluation in every stone former. Table 4 summarizes the approach to a limited clinical and laboratory evaluation. A stone should be analyzed by X-ray crystallography or infrared spectroscopy.

Recurrent Stone Formers

The increased likelihood of relapse during medical therapy makes the multiple stone former a candidate for comprehensive evaluation. Also, if limited evaluation shows presence of a risk factor or presence of active disease (recurrent stone, enlargement of stone, passage of stone gravel in the urine), a comprehensive evaluation should be done. Those with a family history of stones, bone disease, gout, chronic UTI or nephrocalcinosis should also be evaluated in this manner. In recurrent stone formers, full evaluation detects metabolic abnormalities in 96 percent of patients. One study estimated a saving of \$2000/yr as a result of the evaluation.

In addition to the studies suggested for limited evaluation, the comprehensive evaluation includes 24-hour urine studies (preferably on 3 different occasions) to detect presence of supersaturation of stone forming ions in the urine. The evaluation should be delayed for at least three months after a stone event. First two specimens are collected on random diet. Third specimen is collected on restricted diet, with fasting and calcium loading. Urine volume, calcium, phosphate, uric acid, oxalate, citrate, cystine, magnesium, sodium, and creatinine should be measured. Bone density should be checked in the presence of hypercalcemia or hypercalciuria. Normal values of 24-hour urine excretion of various ions are presented in Table 5.

Treatment of Risk Factors

General measures to decrease the concentration of urine, and decrease the excretion of stone forming ions should be taken in all stone formers. Further treatment of stone disease should be individualized based upon the findings of evaluation. Specific measures may result in cure, such as in those with primary hyperparathyroidism.

General Measures

Dietary Modification

A low urine volume is the primary risk factor for stone formation. In a population based study, a small increase of 250 ml in 24-hour urine output was associated with lower rate of recurrence. A study of increased fluid intake in first time calcium stone formers also showed a decrease in recurrence in the intervention group. The rate of recurrence was 27 percent for usual fluid intake patients, and 12 percent for the intervention group. It is advisable to recommend drinking enough liquids to produce two liters of urine per day. Since short periods of concentrated urine can still lead to recurrence, it is important to keep urine dilute at all times. This requires water intake during the night and during periods of physical exertion.

Table 4. Limited evaluation of first-time stone former

History	*Finding*	*Implications*
Diet	Low fluid intake High salt intake High animal protein intake High calcium/oxalate intake	Increased risk, need full evaluation, and specific intervention
Medicine intake	Triamterene, uricosuric agents, calcium containing antacids, vitamin D, calcium-channel blockers, vitamin C, acetazolamide, theophylline, furosemide, acyclovir, indinavir, methyldopa	
Activity of disease	Number and size of stones on imaging, passage of gravel in urine	
Presence of other risk factors	Recurrent UTI, inflammatory bowel disease, gout, neoplasm, sarcoidosis, hyperthyroidism, hyperparathyroidism, RTA	
Previous stone	Results of analysis, surgical intervention	
Examination	Evidence of disease that is considered risk factor, blood pressure, bone disease	Increased risk
Laboratory studies		
Urinalysis	pH of first void urine-	
	Alkaline	RTA
	>7.5	Infection associated stone
	< 5.5	Gouty diathesis
	Crystalluria	Indicates type of stone
Urine culture	Pyuria, urea-splitting bacteria	Urinary tract infection
Cyanide-nitroprusside test	Positive	Cystinuria
Blood biochemistry	High calcium (checked twice) and PTH, low phosphorus	Hyperparathyroidism
	High uric acid	Myeloproliferative disorder, gout
	Normal anion gap, low CO_2 and potassium	RTA
	High BUN, creatinine	Abnormal renal function
Stone Analysis	Specific type of stone	Specific risk factors
Radiologic Study	Radio-opaque or radiolucent stone, number, size	Formulation and follow-up of therapy

Table 5. 24-hour urine stone study-normal values

	Males	*Females*
Calcium*	<300 mg	<250 mg
Uric acid	<800 mg	<750 mg
Citrate	450-600 mg	650-800 mg
Oxalate	<45 mg	<45 mg
Cystine**	<30 mg	<30 mg
PO_4 <1300 mg, sulfate<30 mmol and Mg>50mg/day		

*(spot urine cal:cr ratio x 1.1 estimates 24 hr excretion)
**(maximum cystine solubility is ~250 mg/L)

Different types of fluids may have varying effects on stone recurrence. Population studies have shown reduction in stone risk with most fluids. These include coffee, tea and wine. Lemonade, with its high citrate content may be a preferable liquid, but associated caloric intake may limit intake of large amounts. Grapefruit juice intake was associated with an increased risk of kidney stones in the Nurses Health Study. Intake of colas, probably due to their phosphoric acid content and low pH, has been associated with increased risk of stone recurrence.

Animal protein intake and high sodium intake tend to increase calcium excretion in urine and should be restricted. A recent five-year trial of men with hypercalciuria and recurrent calcium oxalate stones showed a 49 percent reduction in recurrence with a diet normal in calcium and low in animal protein and salt. Oxalate containing foods (spinach, rhubarb, chocolate, nuts, iced tea, etc.) and excessive vitamin C intake should be avoided. Normal calcium intake in diet is associated with lower risk of stone disease. However, the role of calcium supplements is unclear and should be used with caution. Calcium intake should be kept normal (1 to 1.2 gm/day). Restriction of calcium intake is not recommended. If bone disease is present, calcium restriction may be especially harmful.

Cranberry concentrate tablets are marketed for urinary tract health. They have been shown to increase urinary oxalate levels. Patients at risk for nephrolithiasis should avoid these supplements.

Treatment of Risk Factors

Hypercalciuria

Hypercalciuria (excretion of more than 0.1 mmol/kg/day calcium in urine) is present in about 60 percent of calcium stone formers. The hypercalciuria is idiopathic 95 percent of the time. It is occasionally secondary to an endocrine disorder (Table 2). Increased absorption of calcium in absorptive hypercalciuria leads to high serum calcium, calciuria and feedback inhibition of PTH. Type 1 absorptive hypercalciuria is characterized by high calcium excretion on fasting and restricted calcium diet. Type 2 absorptive hypercalciuria demonstrates fasting hypercalciuria, which normalizes upon calcium restriction. Renal hypercalciuria is usually associated with mildly elevated serum parathyroid hormone level.

Thiazide diuretics, such as trichlormethiazide 4 mg daily, with potassium citrate 20 mEq twice daily, are effective in decreasing hypercalciuria due to stimulation of renal absorption of calcium. Those with type 2 absorptive hypercalciuria usually need lower doses of thiazide and potassium citrate. Indapamide 2.5 mg daily is considered as effective and is well tolerated. Sodium intake should be restricted. Absorptive hypercalciuria may benefit from oral orthophosphate (Neutra-phos K, 500 mg three to four times daily) to bind the calcium and decrease the absorption. Sodium Cellulose PO_4 (ion exchange resin- Calcibind, 5 gm powder twice daily with meals) can be used in those with thiazide intolerance or resistance.

Hypocitraturia

Citrate binds to calcium and decreases supersaturation of calcium oxalate. Hypocitraturia is present in 20 to 60 percent of stone formers. Supplementation with citrate can decrease recurrence, even in those with thiazide resistant stones. The preferred agent is potassium citrate (e.g., Urocit K, Polycitra K, 20 to 40 mEq bid). Intake of citrus fruits and their juices should be encouraged.

Hyperuricosuria

Uric acid is a product of purine catabolism and can result from excessive protein intake, known as purine gluttony. Systemic diseases such as gout and myeloproliferative diseases with high cell turnover can result in high uric acid levels and uricosuria, which promotes formation of calcium and uric acid stones. Hereditary conditions (hypoxanthine guanine phosphoribosyltransferase deficiency, glycogen storage disease and excessive activity of glutathione reductase) can also lead to hyperuricosuria.

Uric acid has pKa of 5.35 (i.e., 50 percent of uric acid is soluble and 50 percent insoluble at this pH). Solubility of uric acid increases by 10-fold if the pH of urine is increased from 5 to 6.5. Thus, potassium citrate should be added to keep urine alkaline. Allopurinol 300 mg per day is usually effective in prevention of recurrence of calcium stones associated with hyperuricemia and hyperuricosuria. Those with uric acid stones due to gouty diathesis can be treated similarly.

Hyperoxaluria

Enteric hyperoxaluria results from increased absorption of oxalate in conditions associated with small bowel diseases (Table 2). Dietary hyperoxaluria can be treated with restriction of oxalate containing foods and oral calcium citrate can be used to bind oxalate. Cholestyramine and oral calcium supplements can be used when there is fat malabsorption. Gluten-free diet is beneficial for patients with sprue. A bacterium that degrades oxalate in the gut-oxalobacter formigenes- has also been used.

Hereditary oxalosis due to impaired metabolism of oxalate results in high oxalate excretion in urine, recurrent oxalate stones and renal failure. Urinary glycolate excretion is increased in type 1 and L-glycerate excretion is increased in type 2 primary hyperoxaluria. Stones start forming early in life and can cause renal failure.

Primary hyperoxaluria (type II) and B6 deficiency are treated by increased consumption of liquids, avoidance of oxalate containing foods, supplementation of vitamin B6 and oral orthophosphates (K phos). Stones tend to recur in native and in transplant kidneys. Liver- kidney transplant has been tried successfully, since it repletes the deficient enzyme.

Uric Acid Stones

Uric acid stones are radiolucent and white or orange in color. These are responsible for 5 to 8 percent of all stones in the United States, with a high prevalence (40 percent) in Israel. With normal uric acid excretion, approximately 10 to 20 percent of patients with gout form uric acid stones; the incidence increases to 40 to 50 percent if the uric acid excretion is more than 1 gm/ day. Alkalinization of urine increases solubility of uric acid significantly. Pure uric acid stones can dissolve with alkalinization of urine. Purine content of the diet should be decreased and fluid intake should be increased. Allopurinol prevents recurrence of uric acid stones in those with hyperuricosuria.

Infection-related Stones

Infection associated stones are responsible for 10 to 15 percent of all stones. These are composed of magnesium ammonium phosphate (struvite) or carbonate apatite (triple phosphate). In females, they are mostly pure struvite, but in males these are generally mixed with calcium carbonate apatite. These are also known as urease stones. Struvite stones form in alkaline urine (pH >7.0) due to infection with urea-splitting bacteria, most commonly *Proteus mirabilis*. Splitting of urea results in high urine pH, with associated damage to the glycosaminoglycan layer of the renal pelvis. Stones are large, irregularly laminated and can fill the renal pelvis and conform to that shape, resulting in staghorn calculi. Due to the persistence of infection, usually associated with anatomical or functional abnormality of the urinary tract, these stones are difficult to treat and can result in renal failure.

Treatment of infection in these patients is challenging due to presence of various abnormalities. Prolonged courses of antibiotics with antibiotic prophylaxis for prolonged periods are usually required. A decrease in bacterial colony count from 10^7 per ml to 10^5 per ml reduces urease production by 99 percent, even without eradication of the infection. Urease inhibitors can be used to dissolve struvite stones. Acetohydroxamic acid (Lithostat®, 250 mg three to four times per day) is a urease inhibitor. Unfortunately, it is associated with hemolytic anemia and headache.

Surgical removal of these stones requires combination of lithotripsy and minimally invasive surgery. Combined ESWL/PCNL treatment results in stone free rate of about 80 percent at six months after the procedure. Hemiacidrin (Renacidin®) irrigation of renal pelvis can be done for large stones to facilitate the removal.

Cystine Stones

Cystinuria is an autosomal recessive disorder with a prevalence of approximately 1 in 7,000. Disorders of transport of dibasic amino acids (cystine, ornithine, lysine, and arginine) in the proximal convoluted tubule usually coexist. Poor reuptake of these amino acids results in excessive excretion in urine with normal or low plasma concentration. Homozygous cystinuria is associated with >250 mg per day of cystine excretion in urine, which exceeds the solubility limit. Cystine is poorly soluble and leads to formation of hard, smooth, glistening yellow stones. These may form staghorn calculi. Cystinuria is diagnosed by the presence of hexagonal crystals in urine with high 24-hour urinary excretion of cystine.

Cystine stones are difficult to treat. Dietary restriction of methionine rich proteins (meat, poultry, and dairy), alkalinization of urine to pH >7.0 (with potassium citrate), reduction of sodium intake to <50 mEq/day and increase in urine output to > 3 L/day improve solubility of cystine and may prevent recurrence. D-penicillamine (Cuprimin®) is effective in dissolving 75 percent of cystine stones, but is associated with severe side effects that include agranulocytosis, thrombocytopenia, polymyositis, pemphigus and membranous glomerulonephritis. Treatment should be discontinued as soon as the stone dissolves to prevent development of complications. The dose should be adjusted to keep cystine excretion <200 mg per liter. Vitamin B6 supplementation is needed. Thiola® (tiopronin) and Rimatil® (bucillamine) have less likelihood of side effects and are preferred. Captopril has a sulfhydryl group that binds with cysteine, but is less effective. Chemolysis of cystine stones can be attempted by irrigation of renal pelvis with D-penicillamine or acetylcysteine. The stone may be resistant to lithotripsy due to its hard consistency. For recurrent cystine stones and renal failure, renal transplant will restore the transporter.

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SECTION 7

DIALYSIS AND TRANSPLANTATION

- Technique, Practice and Complications of Hemodialysis
- Principles of Peritoneal Dialysis: Management and Complications
- Immunologic Concepts of Renal Transplantation
- Diagnosis and Management of Post-transplant Medical and Surgical Complications
- Postrenal Transplantation Late Complications Including Rejection

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Technique, Practice and Complications of Hemodialysis

Yijuan Sun, Karen S Servilla and Antonios H Tzamaloukas

This chapter is devoted to hemodialysis as a treatment for end-stage renal disease. Indications and practice of hemodialysis in acute renal failure are presented elsewhere in this book. The modern form of hemodialysis was introduced by Kolff in the early 1940s and constitutes the most common form of renal replacement therapy worldwide. Despite their widespread application and their success in prolonging life, hemodialysis and peritoneal dialysis are limited in their ability to replace renal function primarily providing both excretory and a few synthetic functions, for example of bicarbonate or other simple molecules. Patients on dialytic therapy, therefore, require many dietary and pharmaceutical interventions to manage aspects of renal failure not addressed or incompletely corrected by dialysis. Thus the management of dialysis patients represents a complicated enterprise, which is only partially successful.

PRINCIPLES AND TECHNIQUE OF HEMODIALYSIS

Principles of Hemodialysis

In hemodialysis, the patient's blood is brought in contact with an artificial solution (dialysate) through a semi-permeable membrane. Solute and water transfer through the membrane occur by diffusion and ultrafiltration (Fig. 1). The concentration gradient of solute between blood and dialysate drives diffusion. The diffusion coefficient is a characteristic function of each membrane and determines the amount of diffusion of each solute species for a given concentration gradient. The membrane type and area determine the diffusion coefficient. The composition of blood and dialysate and whether the dialysate contacts the blood only once (single pass) or more than once determine the average concentration gradient during a dialysis session.

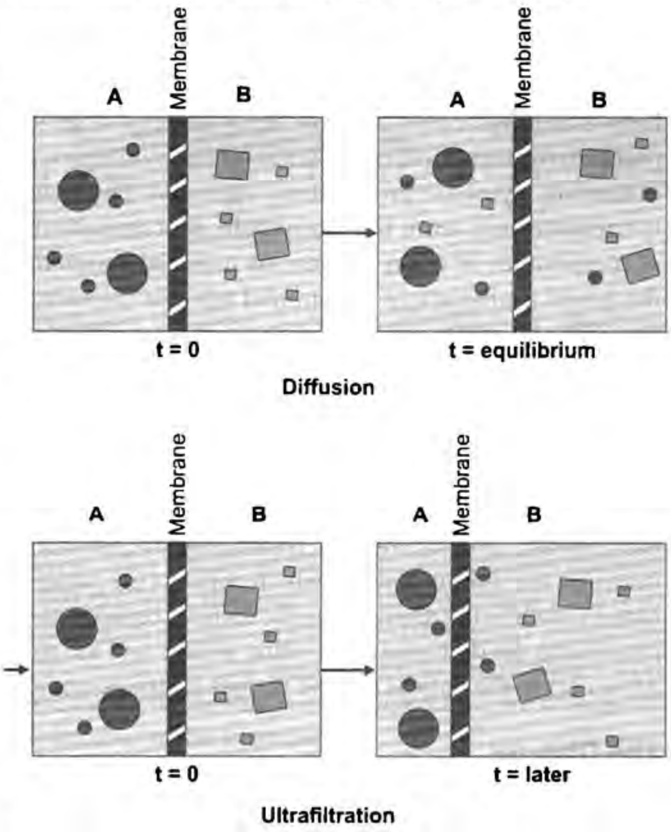


Figure 1: The processes of diffusion and ultrafiltration. (Reproduced wirh permission from Handbook of Dialysis, 3rd Edition. JT Daugirdas, PG Blake, TS Ing, eds. Philadelphia, Lippincott Williams and Wilkins, 2001, p. 16)

The net pressure, the sum of venous and negative pressure, between blood and dialysate compartments is the force driving ultrafiltration. Venous pressure can be changed by varying the hydrostatic pressure in the blood compartment through a clamp on the tubing connecting the device containing the dialysis membrane to the patient's blood vessels. Negative pressure in the dialysate compartment of the device is created by Venturi effect.

Dialysis Membranes

Four types of dialysis membranes are currently in use: cellulose (cuprammonium cellulose, cuprammonium rayon, regenerated cellulose, saponified cellulose ester), substituted cellulose (cellulose acetate, cellulose diacetate, cellulose triacetate), cellulosynthetic (Hemophan), and synthetic (polymethyl-methacrylate, polyacrylonitrile, polysulfone, polycarbonate, polyamide). Coating of membranes with anti-oxidants (e.g., vitamin E) has been used to reduce the oxidative stress caused by hemodialysis.

The membranes differ in physical characteristics (thickness, diffusion coefficient, ultrafiltration coefficient), clearance of middle or large weight molecules (e.g., beta-2-microglobulin, vancomycin), biological effects (heparin consumption, complement activation, leukocyte activation, cytokine production), and cost. The newer membranes are more biocompatible. Biocompatibility of membranes or other exogenous material contacting the blood is absence of or minimal adverse interaction between the material and the blood that would either affect the performance of the device or induce unwanted activation of humoral or cellular cascades.

Dialysis Apparatus

Essential parts of the hemodialysis apparatus include the dialyzer, dialysis solution (dialysate), hemodialysis machine and tubing systems which connect the patient's blood vessels to the dialyzer and the dialyzer compartment containing the dialysate to the water source and the sink. An access to the patient's blood vessels is also essential.

The Dialyzer

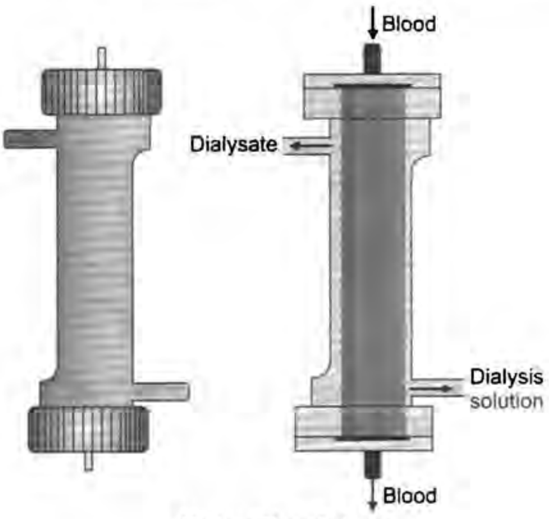
This device contains the dialysis membrane, which is surrounded by a polymethane shell. An efficient dialyzer should have high clearance rates for both small molecular weight toxins, represented by urea, and middle molecular weight toxins, represented by beta-2-microglobulin, but should cause small losses of proteins. Other desirable characteristics of the dialyzers include a high ultrafiltration coefficient with low rate of back leak, small volume in the blood compartment, and biocompatible membrane. As the number of patients on hemodialysis increases worldwides, the cost of the dialyzer becomes more important.

There are three basic dialyzer designs: coil, parallel plate, and capillary. Due to their stability, the latter two designs are more extensively used than is the coil. In these designs blood and dialysate flow in opposite directions (Fig. 2). In the capillary dialyzers the blood flows inside thousands of capillary tubes connected in parallel while the dialysate flows in the compartment surrounding them. Dialyzers currently in use require a relatively small extracorporeal blood volume.

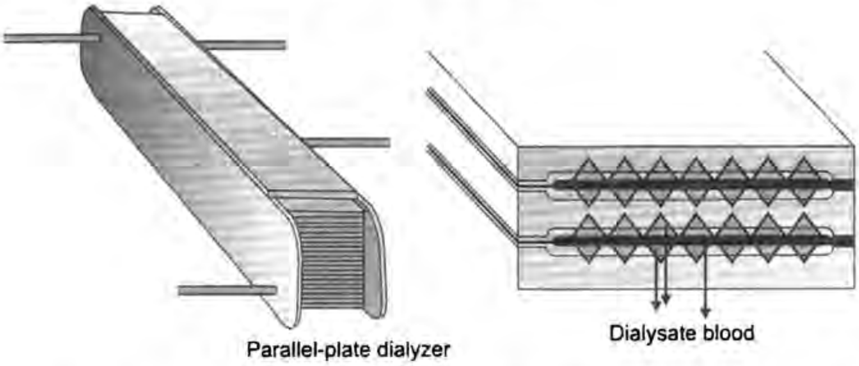
The Hemodialysis Machine

The most commonly used hemodialysis machines mix the dialysate by properly apportioning commercial dialysate bath concentrate and tap water which is purified by a deionizer and a reverse osmosis device. The hemodialysis machine continuously monitors the dialysate composition and temperature, delivers the dialysate to the dialyzer at the desired flow rate, and disposes of the spent dialysate, usually after a single pass through the dialyzer. Alternatively, dialysate can be delivered by a central system mixing dialysate and delivering it to several dialysis machines connected in series. In settings where large amounts of water are not available or easy portability is important, a machine utilizing a minimal amount of water (six liters), can regenerate the dialysate. Spent dialysate passes through columns which either remove azotemic substances by adsorption, or react chemically with dialysate constituents to form dialysate compounds and resynthesize certain dialysate constituents, such as bicarbonate. The major disadvantage of this system is that the delivered dialysis dose, compared to single pass dialysis is less. Newer portable dialysis systems are available and are used for home hemodialysis.

Dialysate composition is variable. In general, azotemic substances (urea, creatinine uric acid, etc.) are absent. Dialysate sodium and chloride concentrations approximate those of normal plasma, and bicarbonate (preferable) or acetate concentration is slightly higher than in normal plasma. Potassium concentration in the dialysate is usually 2.0 mmol/L. The standard



Hollow-fiber dialyzer



Parallel-plate dialyzer

Figure 2: Hollow-fiber and plate dialyzers. (Reproduced with permission from Handbook of Dialysis, 3rd Edition. JT Daugirdas, PG Blake, TS Ing (eds). Philadelphia, Lippincott Williams and Wilkins, 2001 p. 47)

concentrations of potassium, glucose, calcium and magnesium in the dialysate may be modified in accordance with the clinical needs.

The Connecting Tubing System

A system of plastic tubes transfers blood from the patient to the dialyzer and from the water source to the dialyzer. A pump, usually rotary (roller pump), is placed in the arterial blood line (the line bringing the blood from the patient to the dialyzer). The function of the pump is to regulate blood flow rate through the dialyzer. Another line connected to the arterial line delivers to the blood at a designated rate heparin from a syringe mounted on a heparin pump. The venous line is monitored for air bubbles and hemolysis. Adjustable clamps are placed around the venous line to control "venous" pressure (Fig. 3).

Water Treatment

During hemodialysis, the patient's blood gets in contact through the membrane of the dialyzer with a high volume of dialysate (e.g., for a four-hour single-pass hemodialysis session with a dialysate flow rate through the dialyzer of 800 mL/min, the total volume of dialysate getting in contact with the patient's blood is 192 liters). Purification of the water prior to constitution of the dialysate and monitoring of the dialysate composition are critical for the success of the treatment.

Purification of the water has three components, sterility, very low or absent levels of endotoxin, and very low levels of contaminants. Treatment of the water with passage through charcoal filters and either ultrafiltration though special membranes (reverse osmosis), which is the preferred method for removing contaminants, plus meticulous cleansing of the dialysis machines, guided by periodic cultures and checking for endotoxin and contaminants are the mainstay of the water treatment. Contaminants of interest either have documented toxicity in hemodialysis populations (such as aluminum, chloramine, free chlorine, copper, fluoride, nitrate and others) or are known to be toxic in other clinical settings (such as arsenic, lead, cadmium, mercury, etc). Maximal allowed concentrations of these contaminants are periodically published. The maximal allowed levels of contaminants have been reduced considerably in the so-called "ultrapure" dialysate, which is used with increasing frequency, particularly in quotidian (every day) hemodialysis.

The Blood Access

A reliable access to patient's blood vessels is essential to successful long-term dialysis. The lack of such an access causes hemodialysis failure in small subsets of patients even today. The earliest successful system, the Quinton-Scribner shunt, consists of plastic tubing connecting an artery to an adjacent vein, and permits repeated disconnection of the arteriovenous communication and connection of arterial and venous lines to the dialyzer lines. The advent of the Quinton-Scribner shunt allowed the realization of chronic dialysis. However, this type of shunt requires that foreign material placed within a blood vessel also be exteriorized through the skin, and leads to frequent episodes of clotting, infection and accidental disconnection with hemorrhage. For these reasons the Quinton-Scribner shunt is nowadays rarely used for chronic hemodialysis.

The introduction of the arterio-venous (A-V) fistula, an under the skin A-V anastomosis generating large blood flow rates through superficial veins and allowing repeated venipunctures with large bore needles, was another milestone in the realization of widespread chronic hemodialysis. This blood access method has remarkably low rate of complications and is durable in many dialysis patients.

A-V grafts, either synthetic or bovine, are used when A-V fistulae fail (Fig. 4). Grafts can provide satisfactory blood flow rates and have an acceptable life expectancy. However, complications, mainly infections, are generally more frequent with grafts than with A-V fistulae. Unlike A-V fistulae and grafts, permanent subclavian or internal jugular dialysis catheters are associated with high rates of

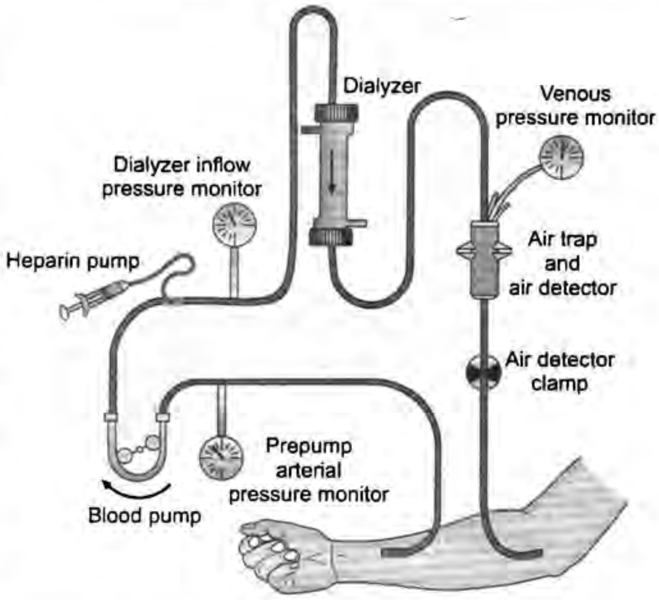

Dialyzer
Venous pressure monitor
Dialyzer inflow pressure monitor
Heparin pump
Air trap and air detector
Air detector clamp
Prepump arterial pressure monitor
Blood pump

Figure 3: Hemodialysis lines and pressure monitors. (Reproduced with permission from Handbook of Dialysis, 3rd Edition, JT Daugirdas, PG Blake, TS Ing, (Eds). Philadelphia, Lippincott Williams and Wilkins 2001, p. 61)

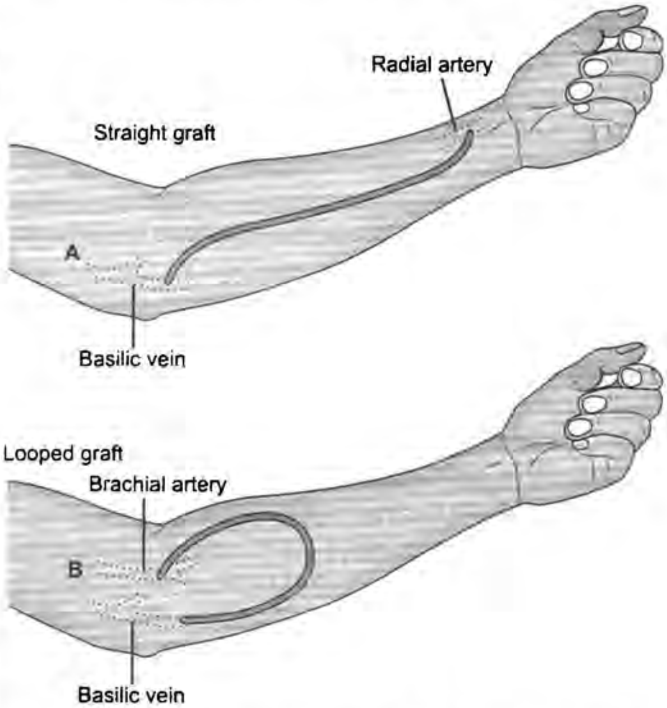


Figure 4: Straight and loop AV grafts. (Reproduced with permission from Handbook of Dialysis, 3rd Edition, JT Daugirdas, PG Blake, TS Ing, (Eds). Philadelphia, Lippincott, Williams and Wilkins 2001 p. 85)

complications both during their insertion (hemothorax, pneumothorax) and during chronic use (infections, clotting of the large veins in the thorax).

As patients starting hemodialysis became progressively older with severe vascular disease, blood access became the major obstacle to hemodialysis. Timely placement of an A-V fistula when hemodialysis is considered for the near future and following of the function of fistulas and grafts with periodic evaluation of blood flow, using various techniques (some incorporated into newer designs of dialysis machines) are important tools for reducing the problems from vascular access.

HEMODIALYSIS PRACTICE

Hemodialysis is performed by inserting two large needles into the A-V fistula, transferring blood to the dialyzer at high flow rates, usually 300 to 500 mL/min, and returning the blood to the patient. Simultaneously, dialysate warmed to body temperature flows through the dialyzer at flow rates equal to 500 to 800 mL/min, contacts the blood through the dialyzer membrane, and is discarded. Blood is heparinized to prevent clotting during the passage through the extracorporeal lines.

The quantitative prescription of dialysis (frequency and duration of dialysis sessions, type and area of the dialysis membrane, transmembrane pressure) is decided by (a) the need to provide adequate solute clearance and (b) prevention of progressive fluid gain. Solute clearance determines the frequency and type of dialysis as well as the size of the dialysis membrane. This prescription of solute crearance is made on a long-term basis. Quantitative changes are made only when clinical needs arise. The appropriate amount of ultrafiltration is determined before each dialysis session and dictates the net ultrafiltration pressure. The deviation of the patient's predialysis weight from a predetermined "dry" weight is dialed into the dialysis machine as the desired ultrafiltration volume. Dry weight is determined early in hemodialysis, usually empirically by progressive reduction of body weight through ultrafiltration until symptoms or signs of extracellular volume depletion develop. This clinical method of determining dry weight is often unreliable and may cause symptomatic hypotension, muscle cramps or more severe ischemic manifestations. Newer methods establishing dry weight, such as bioimpedance measurement or hematocrit monitoring during dialysis, are promising, but have not yet been applied widely in clinical practice. Regardless of the method estimating it, dry weight needs to be re-evaluated frequently during the course of chronic hemodialysis, because patient's nutrition may fluctuate.

Adequacy of Dialysis

The first question related to adequacy of chronic dialysis is when to start dialysis. Guidelines about the management of chronic kidney disease propose estimating glomerular filtration rate (eGFR) from serum creatinine and starting patients on chronic dialysis at eGFR levels around 10 to 15 mL/min per 1.72 m^2 body surface area. A recently published randomized study found no differences in survival or other adverse effects between patients assigned to starting dialysis at eGFR levels of 10 to 15 mL/min and those assigned to start at eGFR 5 to 7 mL/min. However, the majority of the patients in the second group started dialysis at earlier eGFR because of clinical indications. This study may alter some of the current dialysis practices.

After the initiation of chronic hemodialysis, the next question relates to the dose of dialysis that should be considered as adequate. Under usual dialysis schedules the maximal weekly solute clearance is but a fraction of the solute clearance delivered by normal renal function. Both hemodialysis and peritoneal dialysis are, in fact, inadequate renal replacement therapies. Thus efforts directed towards defining dialysis adequacy really address not optimal, but acceptable dialysis.

The gold standard of the assessment of dialysis adequacy had been the relief of clinical uremic manifestations. Since blood level of azotemic indices (urea, creatinine) are believed to have some relation to the level of the uremic toxins, quantitative removal of azotemic indices has been applied as an index of dialysis adequacy. The US National Cooperative Study concluded that the rate of removal of urea is an important determinant of the outcomes of hemodialysis. This finding led to the proposal of an expression of fractional urea clearance during dialysis (Kt/V) as an index of dialysis adequacy. In the formula Kt/V, K represents urea clearance by the dialyzer, t the time of each dialysis, and V the urea volume of distribution, which is equal to body water. Current target Kt/V was set at >1.2 per dialysis session for three-times weekly hemodialysis. A large prospective randomized study (the HEMO study) found no survival advantages with delivered doses of Kt/V higher than 1.20 per session in patients dialyzed three times weekly.

The computation of Kt/V is tedious in hemodialysis, mainly because the calculation of clearance (K) is not simple. Usual methods estimate Kt/V from pre and immediate posthemodialysis blood urea concentration and require computer programs containing complex mathematical calculations. A simpler calculation can be done in any calculator capable of performing natural logarithmic transformation (Ln), as follows:

$$Kt/V = -Ln(R - 0.008t) + (4 - 3.5R)UF/W \quad \{1\}$$

where R is the post-to-pre-hemodialysis blood urea concentration ratio, t is the time of the hemodialysis session in hours, UF is the volume of fluid removed during the hemodialysis session (ultrafiltration) in liters, and W is the postdialysis weight in kilograms.

An easier alternative to Kt/V consists of the calculation of percent reduction of plasma urea concentration during dialysis. It was estimated that a 50-percent reduction of urea concentration is equivalent to a Kt/V equal to 0.8, and that Kt/V increases by 0.2 for each additional 5-percent reduction in urea concentration; the statistical agreement between Kt/V and percent urea reduction was very good. Target urea reduction ratio (URR) is >65 percent.

The use of urea clearance as the only monitor of dialysis adequacy is not meant to replace clinical surveilance for uremic symptoms. Physicians treating dialysis patients should keep in mind that the current target for urea clearance is only a fraction of the clearance delivered by normal kidneys. Subtle uremic symptoms could conceivably develop under current dialysis guidelines. In addition, it is not clear that urea is the best marker of uremic burden. The toxicity of urea is small. It is, therefore, an index of small molecular weight uremic toxins, rather than a toxin. Several middle molecules with specific uremic toxicities have been identified (e.g., beta-2-microglobulin). Middle-molecule clearances, as well as small molecule clearances, will also be used in the future as indices of dialysis adequacy. Other indirect methods assessing dialysis adequacy, such as restoration of intracellular composition to normal or measurement of evoked nerve potentials, have not found widespread application. These indirect methods, based on laboratory evaluation of specific uremic manifestations, will not find extensive application in the era of prevention of uremia.

Modifications of the Dialysis Practice

The introduction of newer dialysis membranes provided the impetus for modifications of basic hemodialysis practice. Dialyzer membranes made of conventional cellulose with high surface areas permitted high-efficiency dialysis, with shortening of the dialysis time. High-flux dialyzers utilize membranes, such as polysulfone, with high permeability to large molecular weight (10,000 to 60,000 daltons) substances, and remove more efficiently azotemic molecules, which may have uremic toxicity, such as beta-2 microglobulin. Newer dialyzer designs including superimposition on conventional dialysis membranes of structures such as membranes constructed by nanotechnology and having pores designed for specific transport processes, for example water channels, or membranes with a line of human proximal tubular epithelial cells grown in culture, may find specific indications in the future. Other modifications of hemodialysis made feasible by special dialysis membranes include continuous A-V hemofiltration, continuous A-V hemodiafiltration, and continuous A-V hemodialysis. Each one of these modifications may have a role, particularly in the management of acute renal failure in unstable patients.

COMPLICATIONS OF HEMODIALYSIS

The complications of hemodialysis can be classified as acute and chronic. Acute complications are unique to hemodialysis and develop during or soon after a hemodialysis treatment. Chronic complications are, for the most part, similar for both hemodialysis and peritoneal dialysis. The conditions described as chronic complications of hemodialysis in this chapter should be considered as complications of peritoneal dialysis also. In addition, the chapter on peritoneal dialysis lists the complications that characterize this dialysis modality alone.

Acute Complications of Hemodialysis

Table 1 shows these complications. Hypotension during hemodialysis is the commonest acute complication, seen in 20 to 30 percent of the dialysis sessions. Its causes are multiple and include acute reduction in blood volume, poor vasoconstrictive responses because of autonomic neuropathies, limited ability to increase cardiac output in response to vasodilatory stimuli,

Table 1. Acute complications of hemodialysis

Hypotension
Muscle cramps
Nausea, vomiting
Headache, chest pain, back pain
Dysequilibrium syndrome
Pruritus
Fever, chills
First use syndrome
Hemolysis
Hemorrhage
Air embolus
Hypoglycemia
Hypokalemia
Dysrhythmia
Cardiac arrest

antihypertensive medications, and vasodilatory factors related to dialysate composition (acetate buffer) and physical properties (high temperature). The presence of severe intercurrent illness causing hypotension, such as pericardial tamponade, myocardial infarction, occult bleeding, sepsis, arrhythmia, or the development of accidents during hemodialysis, such as dialyzed reaction, hemolysis or air embolism, should be systematically investigated, if a patient develops sudden hypotension during dialysis.

Severe dialysis hypotension is managed by temporary interruption of ultrafiltration or even dialysis, placement of the patient in the Trendelenburg position, administration of oxygen by nasal cannula, and bolus infusion of solutions containing hypertonic or isotonic saline, mannitol, or albumin, or administration of midodrine. The most effective measure to prevent dialysis hypotension is minimization of interdialytic weight gains, preferable less than 1.5 to 2.0 kg. Other preventive techniques include sequential use of ultrafiltration and dialysis, temporary increase in the dialysate sodium concentration to 140 to 145 mmol/L in the first half of a dialysis session (sodium modeling), decrease in dialysate temperature to 35 to 36 degrees centigrade, as tolerated by the patient, use of bicarbonate instead of acetate as the dialysate buffer, and use of sympathomimetic agents. In some patients hypotension is severe and persistent and does not respond to manipulation. This situation is most likely due to blunted sympathetic response and may be effectively treated by reducing the duration of dialysis. Sertraline, a serotonin reuptake inhibitor used for the treatment of depression, has been shown to improve autonomic dysfunction and hypotension in hemodialysis patients in one study. Newer hemodialysis machines capable of monitoring blood volume during dialysis and automatically adjusting the ultrafiltration rate offer an effective means of preventing severe intradialytic hypotension.

Muscle cramps, usually in the legs, are also frequent during hemodialysis. The pathogenesis of cramps is unclear, although an association with hypovolemia and dialysis hypotension has been noted. Cramping during dialysis is managed in the same way as dialysis hypotension.

Nausea and vomiting occurring only during hemodialysis is related to dialysis hypotension, the dysequilibrium syndrome, or other dialysis-related syndromes. The prevention of nausea during dialysis includes the prevention of the underlying condition. Antiemetics can be used as symptomatic treatment. Chronic nausea and vomiting occurring regardless of the hemodialysis schedule is also common in dialysis patients and usually signifies intercurrent gastrointestinal disease, or inadequate dialysis. Diabetic subjects on dialysis have a high frequency of gastroparesis and may benefit from prokinetic agents. An investigation of the cause of nausea and an increase in the dialysis prescription are needed in this instance. Peptic ulcer disease should be ruled out. An empirical treatment with H2-blockers or proton pump inhibitors for two weeks may be attempted.

Headaches, chest pains and back pains can be severe during dialysis and have diverse etiologies. Chest pain, in particular, can be a perplexing complaint. Angina pectoris is common in dialysis patients, and occurs frequently during hemodialysis. Reduction of blood pump speed amd nitroglycerin should be tried. In case of severe or persistent chest pain, the hemodialysis session should be discontinued.

The dysequilibrium syndrome was frequent in the early days of chronic dialysis. Nowadays, it is seen during the first few hemodialysis sessions in patients presenting with advanced uremia. The usual clinical manifestations of this syndrome include headache, restlessness, nausea and vomiting. More severe manifestations, such as generalized seizures and coma, are infrequent. The proposed pathogenesis of the syndrome involves rapid decrease in serum osmolality as urea and other solutes are removed by dialysis leading to changes in solute metabolism in the brain cells, with resulting brain edema and changes in cerebrospinal fluid pH. Prevention of rapid changes in blood composition is the best management of this syndrome. Patients presenting with advanced uremia should be started on hemodialysis slowly, with low blood flow rates, short dialysis time, and small surface area dialyzers. If a history of seizures is present, our practice is to load the patients with phenytoin for the first week of hemodialysis.

Pruritus during hemodialysis can be intense and persistent. A specific etiology is usually not identified. Treatment, which consists of antihistamines, moisturizing skin preparations, ultraviolet light, lidocaine infusions is often unsatisfactory. In selected cases, parathyroidectomy has relieved pruritus.

Uremia tends to suppress febrile reactions. The development of chills and fever during hemodialysis may be a manifestation of an underlying infection with temporary improvement in the body's ability to mount a febrile reaction during hemodialysis. Pulmonary and urinary infections are frequent in dialysis patients. Bacteremia and cellulitis caused by skin flora also are seen, particularly in patients with dialysis catheters. *Staphylococcus aureus* nasal carriage, which is common in dialysis patients, appears to be a risk factor for systemic staphylococcal infections. Nasal mupirocin ointment applied periodically (five days in each month) may reduce staphylococcal carriage and infections. Coagulase-negative staphylococci are also a frequent cause of catheter-related infections.

However, chills and fever during hemodialysis can also result from endotoxin formation by Gram-negative bacterial infection contaminating the dialysate. Sterilization of dialysate sources and machines and periodic dialysate cultures are part of the routine maintenance program in hemodialysis units.

Hemolysis from faulty dialysis procedure can occur during or some time after a hemodialysis session and may cause fatal hyperkalemia. Its causes, all preventable, include overheating of the dialysate, low solute concentration in the dialysate, contamination of the dialysate with bleach, chloramine, nitrates, or other contaminants, and improper adjustment of the roller pump used with the arterial line. Free hemoglobin in the blood of the venous line is detected by a hemolysis monitor, which sets off an alarm and shuts down the pump. There are similar detection and alarm mechanisms for air in the venous line. Neither hemolysis, nor air embolus is an acceptable complication of hemodialysis.

Bleeding develops during hemodialysis either externally (around the dialysis needles, or from accidental disconnection of the dialysis lines), or internally, in association with heparinization. Dialysis patients are particularly at risk to bleed from the gastrointestinal tract (often from angiodysplasia of the bowel wall), the retroperitoneal space, renal cysts, and intracranial sites, especially after falls and head trauma. It should be borne in mind that even a trivial trauma, which should be otherwise insignificant, may result in a subdural hematoma in dialysis patients.

Hypoglycemia, either spontaneous or after insulin administration, is common in dialysis patients. If no glucose is added to the dialysate, diabetics with poor glycemic control are subject to life-threatening hypoglycemia during hemodialysis. Addition of glucose to the dialysate, in a concentration of 11 mmol/L, reduces the frequency and severity of hypoglycemia during hemodialysis. While hypokalemia is infrequent before hemodialysis, serum potassium concentration is around 2.8 mmol/L after dialysis, when dialysate potassium concentration is 2.0 mmol/L. Normal potassium levels are attained within the next three to four hours. This transient postdialysis hypokalemia has no adverse effects, except in patients receiving digitalis preparations and those with severe heart disease, who require higher potassium concentrations in the dialysate. Patients with large deficits in body potassium can develop hypokalemia during hemodialysis, even when dialysate potassium concentration is high.

Dialysis membranes, particularly cuprophan, react with blood constituents. Complement activation may lead to changes in leukocytes and to subsequent interactions between leukocytes and endothelial cells. In this instance, blood neutrophil count decreases precipitously in the first few minutes of hemodialysis, and leukocyte aggregations produce multiple microemboli in lung capillaries. Inflammatory cytokines are also released with the use of the same membranes. These phenomena are reversible and are not observed with reuse of the same dialyzer or with some synthetic membranes. The major manifestation of complement activation by the dialysis membrane is hypoxemia. Hypoxemia during hemodialysis, however, may be caused by several other causes including hypoventilation secondary to loss of carbon dioxide in the dialyzer and probably the first use syndrome. Inflammatory cytokines may cause a chronic inflammatory syndrome.

The first use syndrome consists either of an anaphylactic reaction with dyspnea, angioedema, urticaria, gastrointestinal cramps, wheezing and, in advanced cases, cardiac arrest, or of milder nonspecific reactions with chest and back pain. IgE antibodies against proteins altered by ethylene oxide, which is used to sterilize the dialyzers, are found in many patients with anaphylaxis. The management of anaphylaxis consists of immediate discontinuation of dialysis, corticosteroids, antihistamines, epinephrine and cardiac support measures. For less severe symptoms, supportive therapies are required.

Dysrhythmias are common in patients with heart disease, particularly during and immediately after hemodialysis. The prevention and management is specific for each type of dysrhythmia. The dose of several antidysrhythmic agents (Digoxin®, procainamide, etc.) is reduced in dialysis patients. Cardiac arrests during hemodialysis sessions may be caused either by organic heart disease (e.g., myocardial infarction), or by functional causes (hypotension, electrolyte changes). The second category is common during hemodialysis and explains the relatively high probability of survival (approximately 40 percent) after cardiopulmonary resuscitation in the dialysis unit.

Chronic Complications of Dialysis

The chronic complications of hemodialysis are presented in Table 2. These complications may develop in with either hemodialysis or chronic peritoneal dialysis treatments.

Arterial Disease

Hypertriglyceridemia, often accompanied by hypercholesterolemia, is found in between one third and 100 percent of the dialysis patients. The frequency of hyperlipidemia does not differ between hemodialysis and peritoneal dialysis and appears to be mediated by decreased catabolic rate of triglycerides. A low cholesterol diet high in polyunsaturated fatty acids, supplemented by lipid-lowering agents, may be beneficial. Hyperlipidemia is, most probably, the major pathogenetic mechanism of the accelerated atherosclerosis which develops in some dialysis patients. The high incidence of atherosclerosis in dialysis patients leads to severe manifestations of both central and peripheral vascular disease.

Coronary atherosclerosis is a major cause of mortality in dialysis patients. Peripheral vascular disease is manifested by strokes, bowel ischemia and ischemic gangrene of the extremities. Arterial calcifications are common in dialysis patients and increase in frequency with the duration of dialysis. These calcifications are associated with gangrene of both feet and hands, especially in diabetics. Calcification of the coronary arteries in children on hemodialysis was found to correlate with the amount of calcium salt ingested as phosphate binder. The use of oral phosphate binding agents not based on calcium (sevelamer, lanthanum carbonate) is advocated by several experts.

Table 2. Chronic complications of hemodialysis and peritoneal dialysis

Hyperlipidemia, atherosclerosis
Ischemic heart disease
Peripheral vascular disease
Hypertension
Anemia
Osteodystrophy
Extraosseous calcifications
Dialysis dementia
Dialysis amyloidosis
Carpal tunnel syndrome
Degenerative joint disease
Neuropathy
Myopathy
Acquired cystic disease
Endocrinopathy
Chronic infections
Hepatitis
HIV
Malnutrition

Hypertension

Hypertension is very common in dialysis patients. Its mechanisms include salt retention, which may have multiple influences on blood pressure control, increased production of renin-angiotensin, elevated plasma endothelin levels, autonomic nervous system abnormalities, and others, such as hyperparathyroidism. The optimal blood pressure for survival appears to differ between patients on hemodialysis and subjects with normal kidneys, with the first group having better survival at higher blood pressures. Nevertheless, control of hypertension is considered still as important for dialysis patients. First, a reduction of body weight regardless of the presence or absence of peripheral edema should be attempted. This maneuver alone is successful in many instances. If it fails to reduce blood pressure to acceptable levels, or is poorly tolerated, antihypertensive agents should be used.

The choice of agents rests on efficacy and side effects. The superiority of any class of antihypertensive agents for the management of hypertension in dialysis patients has not been convincingly demonstrated. Of note is that angiotensin converting enzyme (ACE) inhibitors have been implicated as a cause of anaphylactic reactions with certain dialysis membranes, particularly those made of polyacrylonite. In addition, resistance to erythropoietin has been described with the use of ACE inhibitors. Finally, use of these agents in dialysis patients is associated with high incidence of severe to life-threatening hyperkalemia. Whether angiotensin receptor blockers (ARBs) are less prone to cause these complications is not clear.

Anemia

The commercial availability of erythropoietin for treatment of anemia in end-stage renal disease has been a major development. Clinicians should remember, however, that in dialysis patients anemia may have many causes, including gastrointestinal bleeding, iron deficiency, folate deficiency if folate loss in the dialysate is not replaced, chronic inflammatory state and occult hemolysis. All these complications are more frequent in dialysis patients than in the general population.

The effects of erythropoietin treatment on the outcomes of dialysis are complex. Studies have shown that erythropoietin does not improve survival in dialysis populations and that the incidence of vascular complications, including cerebrovascular accidents, is higher in dialysis patients reaching normal blood hemoglobin levels under treatment with erythropoietin. The guidelines for the management of anemia in hemodialysis have been revised. Target blood hemoglobin concentration is currently 11 to 13 g/dL.

Osteodystrophy

Osteodystrophy is one of the uremic complications which often progress in dialysis patients. Its two main forms are fibrocystic disease of the bone resulting from hyperparathyroidism, and aplastic bone disease, which was due to aluminum accumulation in most instances in the past, but is seen in a substantial percent of dialysis patients without an aluminum body burden in the present and its causes remain unknown. Some patients have osteomalacia similar to that seen in vitamin D deficiency, and others have a mixed bone lesion. Bone pain, deformities and pathologic fractures are the clinical manifestations of advanced osteodystrophy. Fractures of the femoral neck are particularly serious and should be treated with operative hip fixation, which yields good results even in patients with severe osteopenia.

Hyperparathyroidism is managed by control of serum phosphorus with oral phosphate binding agents such as aluminum hydroxide gel or capsule with meals (for only brief intervals because of the risk of aluminum toxicity), calcium salts, sevelamer carbonate, or lanthanum carbonate. Oral and, in resistant cases, inravenous calcitriol or one of the analogs of vitamin D2 or D3 are helpful in controlling hyperparathyroidism and should be started early in the course of renal failure. Cinacalcet, a compound binding to the extracellular calcium receptor and increasing its sensing of calcium thus inhibiting parathyroid hormone secretion, has reduced the need for parathyroidectomy, which may be required in cases of intractable cystic fibrosis of the bone, progressive myopathy, persistent hypercalcemia, or severe hyperphosphatemia in the setting of adequate phosphate binder use. This may arise from extremely high parathyroid hormone levels resulting in phosphate release from bone. If bone biopsy suggests aluminum-induced aplastic bone disease, in which parathormone (PTH) blood levels are frequently normal or low, serum aluminum levels should be measured before and after administration of desferoxamine. If serum aluminum levels are high, the patient should be treated with intravenous desferoxamine

1 gm per week for three to four weeks. The treatment effectiveness is monitored by serum aluminum levels.

Extraosseous Calcifications

The abnormal calcium and phosphorus metabolism in dialysis patients can lead to extraosseous calcifications usually involving the tunica media of the arteries and associated with ischemic events, at least in diabetic subjects. Visceral calcifications, in the heart, lungs, kidneys, stomach, etc, primary related to hyperparathyroidism and to high calcium-phosphorus product, are associated with serious organ dysfunction. Nonvisceral calcifications, primarily in subcutaneous and periarticular tissues, are also considered to result from high calcium-phosphorus product and have been linked to hyperparathyroidism. Nonvisceral calcifications have also been linked to aplastic bone disease and to high endogenous calcitriol levels.

Calciphylaxis (calcific uremic arteriolopathy) is seen in a small number of dialysis patients. It is histologically characterized by calcifications in the wall of small vessels, intimal hypertrophy, small vessel thrombosis and panniculitis. Clinically, it is manifested by usually bilateral, very painful violaceous plaques starting in the lower extremities and spreading to the rest of the body. Ulceration of the plaques is associated with high mortality, mainly from superimposed infections. In addition to abnormalities of the calcium-phosphorus-parathyroid hormone access, chronic inflammation, which affects several inhibitors of calcification, has been implicated in the pathogenesis of calciphylaxis. The treatments applied have had no great success. Intravenous sodium thiosulfate has givem some promising results.

Dialysis Dementia

Aluminum accumulation in the body causes at least two clinical syndromes: Aluminum bone disease was already discussed. Dialysis dementia which was described by Alfrey, is manifested by speech disorder (dysarthria, dyspraxia), myoclonic jerks, motor apraxia, seizures, and a characteristic electroencephalogram, and is believed to result from aluminum loading, particularly from dialysate made with tap water high in aluminum. The removal of aluminum from the tap water by the reverse osmosis technique has reduced greatly the incidence of dialysis dementia.

Dialysis Amyloidosis

A unique form of amyloid deposition occurs in tissues of dialysis patients. The amyloid fibrils consist almost entirely of beta-2 microglobulin, which is a middle molecular weight protein attached by sulfhydryl bond to the main molecule of the HLA transplantation antigen, a large protein embedded in the cell membrane of leukocytes, monocytes, etc. Beta-2 microglobulin is released in the blood as leukocytes are destroyed, and is normally excreted by the kidneys. In dialysis patients, however, its blood concentration increases to over 30 times the normal levels, and this results in amyloid deposition in several body tissues. The main clinical manifestations of dialysis amyloidosis consist of destructive arthropathy, periarticular disease, carpal tunnel syndrome and pathologic bone fractures. Blood levels of beta-2 microglobulin are similar in hemodialysis and peritoneal dialysis patients. Clinical manifestations of amyloidosis have been found in both dialysis modalities. However, polysulfone dialysis membranes are permeable to this molecule and with their use a reduction of the incidence of dialysis amyloidosis can be expected. A subtantial reduction of serum beta-2-microglobulin levels was reported in patients on quotidian night-time hemodialysis.

Carpal Tunnel Syndrome

Carpal tunnel syndrome in dialysis patients has several pathogenetic mechanisms, including dialysis amyloidosis and hemodynamic effects of the A-V fistula. This syndrome is asymptomatic in many dialysis patients and is diagnosed by nerve conduction studies. If left untreated, carpal tunnel syndrome leads to progressive dysfunction of the hands. Surgical decompression of the median nerve is the most effective management of this syndrome, which, unfortunately, recurs in some dialysis patients. Degenerative joint disease has multiple etiologies in dialysis patients.

Neuropathies and Myopathies

Neuropathies are common in dialysis patients. Uremic polyneuropathy is usually arrested by adequate dialysis, but does not improve. Diabetic neuropathy, often affecting the autonomic nervous system, progresses during dialysis and causes severe disabilities. Dialysis patients may also develop treatable neuropathies, such as those caused by toxins (ethanol, lead), or nutrient deficiencies (vitamins). A search for reversible causes and a reevaluation of the adequacy of dialysis are warranted when neuropathies progress. In dialysis patients, a form of severe proximal myopathy is associated with hyperparathyroidism and can be managed with calcitriol in a dose of 0.25 mcg daily. Calcitriol administration contiues indefinitely, unless severe hypercalcemia or progressive extraosseous calcifications develop. Parathyroidectomy should be restricted for subjects developing these complications. Acute myopathies, which can precipitate life-threatening hyperkalemia, can be caused by some lipid lowering agents, such as gemfibrosil and lovastatin.

Respiratory Problems

Dialysis patients have increased risk of tuberculosis. In addition, sleep apnea is frequent in patients on either hemodialysis or peritoneal dialysis.

Acquired Renal Cysts

The scarred kidneys of patients on long-term dialysis may develop cysts. The frequency of this acquired renal cystic disease increases with the duration of dialysis. Major complications of these renal cysts consist of bleeding and malignant degeneration, which is uncommon.

Endocrinopathies

Prolonged dialysis is associated with several endocrinopathies. Gonadal dysfunction is almost universal. Hypothyroidism presents diagnostic difficulties, because renal failure independently affects thyroid function tests. The newer, sensitive serum thyrotropin or thyroid-stimulating hormone (TSH) assays have facilitated the detection and management of hypothyroidism. Abnormalities in the adrenal and pituitary functions have also been described in dialysis patients.

Infections

Infections in dialysis patients constitute a major cause of morbidity. Multiple defects in host resistance have been described. Chronic infections, such as tuberculosis, are more frequent in dialysis patients than in the general population. Two chronic viral infections warranting special attention in dialysis patients are viral hepatitis and HIV infection. In the early days of dialysis, when patients required multiple blood transfusions, hepatitis B presented a major health risk for both dialysis patients and staff. The decrease of the need for transfusions and the introduction of an effective hepatitis B vaccine have considerably reduced the risk of hepatitis B in dialysis units. It should be noted, however, that dialysis patients develop lower antibody titers than normal subjects, have a high rate of conversion to an antibody-negative status, and may require higher doses and periodic booster doses of the vaccine. Several dialysis units have reported an increasing prevalence of hepatitis C in dialysis patients as time on hemodialysis increases. The risk of transmission of HIV in dialysis units is small.

Malnutrition

Malnutrition develops frequently in dialysis patients. It is often associated with chronic inflammatory syndromes and increases the risk of infection and mortality from all causes. Nutrition guidelines for hemodialysis patients have been published.

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Principles of Peritoneal Dialysis: Management and Complications

Jose A Diaz-Buxo, Rainer Himmele

Peritoneal dialysis (PD) was first used for the treatment of uremia in humans in 1923, but it was mostly reserved for the treatment of acute renal failure until the 1970s when a permanent peritoneal access and automated equipment became available.[1, 2] Continuous ambulatory peritoneal dialysis (CAPD) was introduced in 1976.[3] Since then, many modifications to the original technology have been introduced and the proportion of patients undergoing PD has grown dramatically. Given a global prevalence rate of PD of 27 per million population (pmp) and a world population of 6.6 billion, an estimated number of 187,200 patients were maintained on chronic PD in 2007.[4] The utilization of PD varies widely in different countries probably reflecting reimbursement practices and cultural differences with generally higher prevalence rates in developed countries. In 2008, the US prevalence rate for PD was 83 pmp with a total of 26,517 PD patients.[5]

PHYSIOLOGY OF THE PERITONEAL MEMBRANE

The peritoneal membrane is more of a physiologic concept than a single anatomical structure. It consists of the peritoneum and its associated blood supply. These two cell layers, the capillary endothelium and the peritoneal mesothelium, build one functional unit: the peritoneal membrane. Its effective surface area correlates with body surface area in adults and children.[6, 7, 8] Functional concepts of the peritoneal membrane suggest that the peritoneal capillary, and to a lesser extent, the interstitium build the main barrier to peritoneal transport.[9] The mesothelial cell layer itself is of minor importance. Based on experimental evidence, a three-pore model of the peritoneal membrane was established to focus on the functional importance of the capillary permeability and selectivity on fluid and solute transport across the peritoneal membrane.[10-13] The model describes three pathways of water and toxin removal with large, small and ultra-small pores. Large pores have a size of 10-20 nm (100-200 A) and are anatomical clefts between endothelial cells. Although they constitute only <0.1% of total pores, they account for removal of up to 10% of solute and most of the macromolecules. Small pores have a diameter of 4-6 nm (40-60 A) and are smaller intercellular clefts. They are more numerous and account for >90% of solute removal. While large and small pores eliminate water and solutes, the ultra-small pores do not clear solutes, but are transcellular water channels called Aquaporins in the endothelial wall. They range in size from 0.4-0.6 nm (4-6 A). Given the central role of the endothelium, the degree of vascularity of the peritoneum is the primary determinant of the peritoneal transport characteristics. Vascularity is a measure of the number of capillaries and their perfusion determines the relevant effective blood flow for peritoneal dialysis. The influence of each capillary on peritoneal transport depends on its perfusion and proximity to the peritoneal mesothelial cell layer, which constitutes the blood-dialysate interface.

The described transport characteristics of molecules through large, small and ultra small pores lead to a clinically relevant phenomenon referred to as sodium sieving. PD solutions have a sodium concentration (typically around 134 mEq/L), "that" is only slightly below plasma levels, which prevents effective diffusive sodium elimination. Therefore, a significant amount of sodium is removed through ultrafiltration. However, this may seem counterintuitive since UF is primarily accomplished through the aquaporins, which only transport water. However, sodium is held back (or sieved) at the aquaporin level, while water moves through.

The rate of sodium sieving depends on hypertonicity of the dialysate and dwell time. Sodium sieving is less in CAPD with longer dialysate dwell times because the contribution of aquaporins to ultrafiltration is less important and enough time is given to sodium equilibration. On the contrary, during short dwells with hypertonic dialysate, more water than sodium is removed from the extracellular volume thereby creating an imbalance that may lead to hypernatremia or elevated sodium ion concentration in blood serum.[12, 31] This especially applies to not previously defined APD with frequent short cycles.[32]

Low sodium dialysates (98 to 125 mEq/L)[29] have been investigated with promising results but are not commercially available.[30]

PERITONEAL SOLUTE AND WATER TRANSPORT

Peritoneal transport is comprised of four simultaneous processes. The main driving forces are diffusion and osmosis, whereas convection and fluid absorption play an important but secondary role.

Solute removal takes place by diffusion, driven by a concentration gradient between the blood compartment and intraperitoneal dialysate. Diffusive transport of solutes occurs through the small and large pores and is effective for molecules that are usually not contained in the dialysate, e.g., creatinine, urea, potassium, phosphate, and other uremic toxins. Diffusive transport is not effective for molecules that are contained in the dialysate in almost similar concentrations to serum such as sodium or calcium. Diffusive solute removal further depends on the molecular size of the toxin where larger molecules are less effetively removed.

Water elimination is achieved mainly through the small pores and aquaporins as a result of the osmotic gradient between the relatively hypertonic dialysis solution and the relatively hypotonic peritoneal capillary blood. The higher the osmotic gradient, the higher is the ultrafiltration. In PD, the osmotic pressure is the equivalent of the hydraulic pressure used to achieve ultrafiltration in hemodialysis machines. The osmotic gradient is most commonly obtained through the use of different concentrations of hyperosmolar glucose in the dialysate. Due to the bi-directional flow of glucose molecules across the peritoneal membrane, the ultrafiltration rate is greatest at the onset of the exchange and falls exponentially as glucose equilibrates. Thus, shorter and more frequent dialysate exchanges with hypertonic solutions result in greater ultrafiltration and proportionally less glucose absorption.[14] For special indications, alternative osmotic agents such as polyglucose or aminoacids can be used.

Convection is the transport of solutes that occurs together with the movement of water driven by the osmotic gradient. It takes places mainly through small pores but not through the aquaporins, redundant phrase are exclusively water channels. Convection is important for the removing of molecules that are mainly eliminated through ultrafiltration due to the absence of an osmotic gradient, for example sodium.

Fluid absorption occurs during dialysis through lymphatic absorption and direct absorption into tissues. The reported rate of fluid absorption is about 1-2 ml/min, which is believed to reduce cumulative net ultrafiltration by 50 to 80%.[15, 16] Intra-abdominal lymphatics are therefore an important determinant of the achieved net ultrafiltration.[17, 18] Although the abdominal cavity is very rich in lymphatic drainage, the subdiaphragmatic lymphatics have been identified as the most important reabsorptive system.

ASSESSMENT OF PERITONEAL MEMBRANE CHARACTERISTICS

A very useful tool to categorize solute transport rates in individual patients is the peritoneal equilibration test (PET).[19] This simple study consists of instilling two liters of a standard 2.5% dextrose dialysis solution intraperitoneally and letting it dwell for four hours. A blood sample midway during the procedure, or the average of an initial and final blood sample, is used to determine plasma concentration of the solute. Peritoneal dialysate samples are obtained periodically during the four hours. At the end of the exchange, the remaining volume is drained and measured accurately. Over the four hours, glucose will be absorbed from the dialysis solution. This is quantified by the ratio of glucose concentration at the time of measurement compared to that at the start (D_t/D_o). In contrast to glucose, the solutes and toxins will increase in the dialysis solution over time until fully equilibrated with plasma levels. Dialysate to plasma ratios (D/P) for the different solutes are determined and plotted. Depending on the rate at which glucose and solutes equilibrate, patients can be classified as slow (low), average or fast (high) transporters compared to the average transport rates of a reference population (Figure 1). The assessment of the patient's membrane transport characteristics (by PET) is of utmost importance to determine the optimal PD modality and prescription. It has also proven useful in evaluating potential structural or functional changes of the peritoneal membrane over time on dialysis.

PERITONEAL DIALYSIS ACCESS

Peritoneal dialysis depends on a reliable peritoneal access for the inflow and outflow of the dialysis solution. The goal is to achieve an optimal and consistent hydraulic function, a stable interface between catheter and body, and minimal complications with low maintenance.

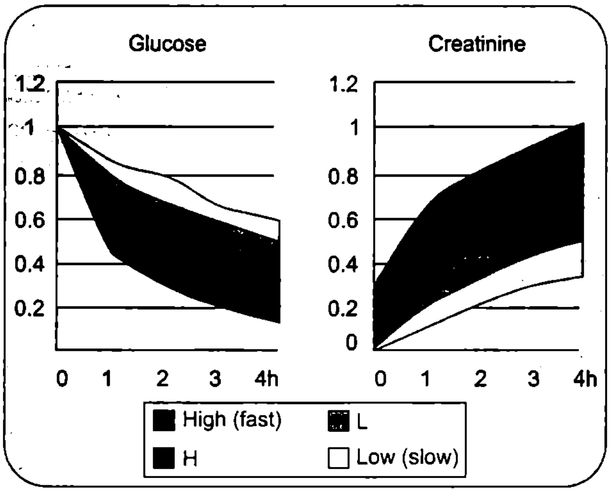


Figure 1: Peritoneal equilibration test (PET)
Classification of transport characteristics according to the peritoneal equilibration test (PET). The graphs show the dynamics of glucose absorption and creatinine excretion over time on dialysis. Low (slow) transporters need considerably longer to reach similar equilibration than high (fast) transporters.

Most of the commonly used catheters follow the design introduced by Tenckhoff and Schechter in 1968 featuring a straight or a curled intraperitoneal end with multiple side holes and one or two Dacron cuffs to seal the subcutaneous tunnel.[2] A great selection of PD catheters are commercially available including the traditional one or two cuff, straight or curled Tenckhoff catheter; swan-neck varieties, which incorporate a permanent bend for the subcutaneous segment of the catheter; those with disks and balloons designed to reject bowel loops and omentum around the intra-abdominal segment of the catheter; and catheters offering larger pore size and surface area designed to enhance dialysate flow. Silicone is the most frequently used material and is free of leachable plasticizers. Polyurethane is a stronger material that allows thinner-walls with larger lumen at the same outside diameter. However, polyurethane is prone to cracking after exposure to alcohol or polyethylene glycol-containing containing substances such as Mupirocin, which is often used for local infection prophylaxis. While the materials of the catheter are selected for optimal bioincompatibility, the Dacron felt cuffs are made of bioincompatible material that promotes fibrosis and tissue growth in order to ensure sealing of the subcutaneous tunnel and anchoring of the catheter in the abdominal wall.

Catheter placement by either a nephrologist or a surgeon can be achieved with the use of a trocar, a Seldinger guide wire technique, peritoneoscopically or under direct surgical visualization.[20, 21] As a variation of the standard procedure, the external part of the catheter can remain buried in the subcutaneous tissue for several weeks or months in order to secure a better seal at the level of the external cuff.[22] The preferred technique for placement varies according to the physician's preference and experience. The best practices for optimal peritoneal catheter practices have been summarized and published by the International Society of Peritoneal Dialysis (ISPD).[23, 24] The intra-abdominal segment of the peritoneal catheter should be directed towards the left lower quadrant and specifically into the rectovesical pouch, which is normally the most dependable location in the pelvis.[25] An arcuate subcutaneous tunnel with a caudad oriented exit is recommended in order to facilitate drainage of the exit site, prevent accumulation of sweat, bacteria and debris, and thus reduce exit site infection. Some clinicians recommend a seven- to fourteen-day waiting period to ensure good tissue healing and to prevent early dialysate leaks following the insertion of a peritoneal catheter, while others prefer the immediate use of the catheter.[20] Immediate catheter use is appropriate, if a low exchange volume is applied and the patient is kept in the supine position in order to reduce *intra-abdominal* pressure and prevent dialysate leaks. While each methodology of catheter placement has its specific attributes, recent studies seem to indicate that surgical laparoscopic techniques may have less complications such as leaks or flow dysfunction.

The most common complications resulting from catheter insertion are pericatheter dialysate leaks, catheter cuff extrusion, exit-site infection, tunnel infections, vessel or visceral perforation, hernia formation, hydrothorax, hydrocele and catheter obstruction.[26, 27] Catheter obstruction can be total (inflow and outflow) or limited to outflow failure. The latter is the most common and problematic type. This is usually the consequence of peritoneal wrapping around the intra-abdominal segment of the catheter resulting in a ball-valve effect.

PERITONEAL DIALYSIS SOLUTIONS

The standard PD fluid consists of three components: Electrolytes, an osmotic agent and the buffer. The electrolytes usually contained in PD solutions are sodium, calcium, magnesium, and chloride. Optimal electrolyte composition of a dialysis solution varies depending upon the treatment modality, on the osmotic agent being used, and also on dwell time.[28, 29] The ideal electrolyte composition is that which best serves the homeostatic needs of the body. Common osmotic agents include glucose, polyglucose, and amino acids. The buffer is necessary to correct metabolic acidosis. Common buffers are lactate or bicarbonate. Acetate is no longer used as a buffering agent.

Conventional PD solutions contain electrolytes, glucose and buffer in one single chamber bag. During heat sterilization of the solution, caramelization of glucose occurs resulting in formation of toxic glucose degradation products (GDPs).[33] GDPs may also be formed in PD solutions during storage for long periods of time[34, 35] or at elevated temperatures.[36] Since GDP formation is worst when sterilized at high pH, the pH of conventional solutions has been lowered to an acidic pH of 5-6. However, this causes some bioincompatibility of the solutions.

The toxic potential of GDPs derives from their ability to form advanced glycation end products (AGEs), i.e., binding of a sugar molecule to either a protein or lipid without an enzyme catalyst.[37] AGEs may form endogenously in serum and in tissues through normal metabolism and aging[38] but can significantly increase under certain conditions, such as oxidative stress due to hyperglycemia in diabetic patients or due to uremia in dialysis patients. AGEs are potent stimulants for inflammatory responses and amplify oxidative and free-radical chemical pathways. Excess of AGEs has been implicated in uremic and diabetic vascular disease, which causes significant morbidity and mortality in dialysis patients.[37]

New, more biocompatible PD solutions have been developed with substantially lower GDP content and neutral pH. This has been achieved by the use of double-chambered bags featuring one acidic compartment for glucose and electrolytes and an alkaline for the buffer agent. This allows heat sterilization of glucose at an optimal pH with minimal GDP formation. Moreover, keeping the electrolytes in the acid compartment prevents precipitation of calcium and magnesium. Prior to use, the wall between the two chambers is broken and the two solutions are mixed, resulting in a solution with a physiologic, neutral pH and low GDPs. Other innovative approaches substituted glucose using polyglucose and amino acids as osmotic agents. These solutions also show low levels of GDPs but still have an acidic pH. Biocompatible solutions have been proven safe and effective. However, these solutions are not approved and available in all countries. A comparison of conventional and new solutions is shown in table 1.

MODALITIES OF PERITONEAL DIALYSIS

The modalities of PD can be broadly divided into continuous and intermittent treatment. A further distinction is if the dialysate exchanges are performed manually or using a dialysis machine, referred to as peritoneal dialysis cycler. The two most common modalities are Continuous Ambulatory Peritoneal Dialysis (CAPD), which is done manually and Automated Peritoneal Dialysis (APD), which uses an automated cycler for the exchanges.

Table 1. Comparison of conventional and new PD solutions.
Various PD solutions are commercially available with distinct differences in osmotic agent, buffer substance and pH (All glucose expressed as hydrous glucose).

Name	*Osmotic Agent*	*Strengths (%)*	*Buffer (mmol/L)*	*pH*
Delflex® Conventional	Glucose	1.5, 2.5, 4.25	Lactate	~5.5
Delflex® NpH	Glucose	1.5, 2.5, 4.25	Lactate	7.0
Bicavera®	Glucose	1.5, 2.5, 4.25	Bicarbonate	7.4
Balance®	Glucose	1.5, 2.5, 4.25	Lactate	7.0
Gambrosol Trio®	Glucose	1.5, 2.5, 3.9	Lactate	5.5-6.5
Physioneal®	Glucose	1.5, 2.5, 4.25	Lactate & Bicarbonate	7.4
Extraneal® (Icodextrin)	Polyglucose	7.5	Lactate	5.0-6.0
Nutrineal®	Amino Acid	1.1	Lactate	6.7

Continuous Ambulatory Peritoneal Dialysis (CAPD)

CAPD was first described by Popovich and Moncrief in 1976[3] and in principle is still applied in a similar way. It is based on the concept of a continuous presence of dialysis solution in the peritoneal cavity, interrupted only by the brief periods required for drainage and infusion of new dialysate at the end of the exchange period, which is typically every four to six hours. Due to this low dialysate exchange rate (flow rate) continuous PD results in nearly complete equilibration between plasma and dialysate for small molecules and toxins. Although CAPD has a relative low efficiency compared to other modalities or hemodialysis, the continuous nature of this therapy still allows adequate weekly small molecule clearances as defined by a delivered total weekly Kt/V_{urea} >1.7.[47, 48] For clearance of larger molecules, in the range of 500-15,000 Daltons, longer dwell times are required for equilibration favoring CAPD with longer exchanges over APD; the latter is usually performed with more frequent and shorter exchanges. Various advances in the technology of CAPD have been responsible for its popularity. The use of disposable bags has improved the mobility and independence of the patient. Improvements in connectology between the PD catheter and dialysate bags, specifically in disconnect systems, have reduced the high incidence of peritonitis that initially plagued CAPD.[44, 45] The "flush before fill" effect achieved with disconnect systems probably reduces contamination of the connecting parts and favors a lower rate of peritonitis.[46] The simplicity of the technique has resulted in a short training time, independence from constant supervision and attendance in a dialysis clinic, freedom of mobility and significant reductions in the cost of provision of therapy.

Automated Peritoneal Dialysis (APD)

The terms APD and Continuous Cycling Peritoneal Dialysis (CCPD) are often used synonymously. However, CCPD is a common submodality of APD, since APD is not restricted to continuous cycling. Continuous and intermittent treatment forms are both adequate applications of APD.

Continuous Cycling Peritoneal Dialysis (CCPD) was introduced as an alternative mode of CAPD in the 1980s by Diaz-Buxo and Suki.[49, 50] A cycler is used, usually at night time, to automate multiple cycles of dialysate inflow and drainage after a predefined dwell time for each cycle. The typical CCPD prescription consists of several exchanges during the night and one prolonged day time exchange. The continuous nature of this system provides small molecule clearances similar or higher to those of CAPD and similar clearances for middle molecules. CCPD, may enhance the host's immunologic defenses by allowing repopulation of peritoneal macrophages during the long day dwell.[51-53] Major advantages of CCPD are freedom from exchange procedures during the day, which allows more time for work or recreation. CCPD is also suitable for assisted PD with help from a partner, since connection and disconnection procedures are limited to one in the morning and one at night.

An important modification to CCPD was the addition of a manual or automated exchange during the day to avoid the use of very long dwell times (PD Plus). This prescription reduces dwell time and consequently increases ultrafiltration while avoiding the use of highly hypertonic solutions. It also allows reduction of the number of nocturnal exchanges and results in more uniform exchanges providing with better equilibration of solutes between plasma and dialysate.

Nocturnal intermittent peritoneal dialysis (NIPD) is an intermittent form of APD with cycler-assisted dialysis during the night and an empty abdomen during the day. Similar to other intermittent PD therapies, it has the disadvantage of not providing a steady physiologic state and is associated with lower middle molecule clearances. This technique is mostly reserved for patients with high transport rates and ultrafiltration failure who can benefit from shorter and more frequent dialysate exchanges during the night. However, due to their fast transport rates, glucose in the PD solutions is absorbed rapidly, making long exchanges during the day ineffective. NIPD is also advantageous in patients suffering from hernias, bladder and uterine prolapse, intractable low back pain, restrictive lung disease, gastrointestinal reflux and other conditions associated with increased intra-abdominal pressure, since the abdominal cavity is drained during the day and the intra-abdominal pressure generated by dialysate at night is significantly lower than in the sitting or standing position.

Tidal peritoneal dialysis (TPD): TPD is a form of APD performed without complete drain of the peritoneal dialysis solution before the next inflow. This maintains a constant reserve volume in the peritoneal cavity in addition to the volume cycled in and out of the peritoneal cavity (Figure 2). This technique was designed to enhance solute clearance by improving solute mixing of dialysate and by the constant restoration of the dialysate-plasma gradient with enhancement in peritoneal clearance. Although the initial studies suggested higher small solute clearance compared to other modalities of APD, it was later recognized that the extent of the improvement was partly influenced by higher exchange volumes used with TPD.[58, 59] The primary disadvantages of this procedure are the need for a special cycler and the high dialysate volumes, both of which result in a significant increase in cost.

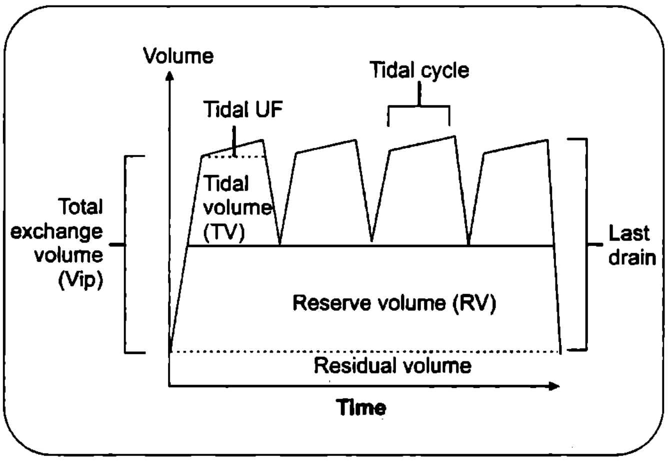


Figure 2: Tidal peritoneal dialysis (TPD)
Four cycles of tidal PD are shown. Total inflow and outflow volumes used only at the first and last exchanges. For other exchanges or cycles, a reduced volume is used leaving a constant reserve volume over the complete time on dialysis.

Intermittent PD (IPD): IPD was extensively used for the treatment of acute renal failure prior to the general availability of hemodialysis (HD) and before the introduction of CAPD and CCPD. The term intermittent PD here refers to the fact that this treatment is not offered to the patient on a daily basis, as opposed the nightly intermittent peritoneal dialysis (NIPD). It is mostly provided as an in-center or hospital PD treatment option with several cycler assisted treatments several days per week. The typical prescription uses a relatively high volume (2-4 L/hour) and frequent exchanges (1-2/hour) for 8-24 hours sessions. This high volume, intermittent therapy results in relatively high small solute ($MW \leq 200$) removal with limited middle or large molecule clearance and high but intermittent ultrafiltration The major drawbacks of this modality are the limited middle molecule clearances, the interdialytic weight gains and the high cost due to large volumes of PD solutions. Although IPD is still used in some countries for the temporary treatment of acute renal failure and for patients with significant residual renal function, the long-term experience suggests a high mortality rates due to insufficient dialysis.[54, 55]

ADEQUACY AND MEASUREMENT OF DIALYSIS DOSE

Adequacy of dialysis can be measured by the clearance of solutes and net ultrafiltration. The concept of Kt/V for the quantitation of dialysis dose has been popularized by

Gotch and is widely accepted as the standard measure for solute removal.[57, 58] The current guidelines define Kt/V as a measure of urea clearance for evaluating adequacy of dialysis dose:[47, 48]

Adequate peritoneal dialysis dose

= minimal delivered total weekly Kt/V_{urea} of >1.7

where K represents urea clearance, t is the time or duration of dialysis and V the volume of distribution of urea. "Total" refers to the combined peritoneal and renal urea clearance, if the patient still has a residual renal function > 100 ml/day. For anuric patients a $Kt/V_{urea} > 1.7$ has to be achieved exclusively with PD.

Measurement of total weekly Kt/V_{urea} is based on a 24-hour collection of the dialysate effluent for CAPD and APD, which is used to calculate the peritoneal Kt/V_{urea}. A 24-hr urine collection is used to calculate the renal Kt/V_{urea}, if volume is >100 mL/d. The total weekly Kt/V_{urea} is the sum of the daily peritoneal and renal urea clearance times seven, divided by the patient's urea distribution volume (V). Because gold-standard isotope dilution techniques are not commonly available, the V is usually calculated using the anthropometric equation described by Watson or Hume-Weyers for adults.[64, 65] Total total weekly Kt/V_{urea} should be measured within the first month after initiating dialysis therapy and at least once every 4 months thereafter. A 24-h urine collection to determine urine volume and renal clearance should be performed at least every 2 months.[48] Due to the declining residual renal function over time on dialysis the peritoneal dialysis dose has to be steadily increased to compensate for the loss of renal clearances.

An alternative established measure is creatinine clearance, which is traditionally normalized to a standard body surface area of 1.73 m^2. Other less commonly applied methods of measuring dialysis dose include the solute removal index[59] and the dialysis index.[60]

Peritoneal solute clearance can be easily calculated using the following formula:

$$\text{Peritoneal clearance} = C_D V_D / C_P T$$

where C_D = concentration of the solute in dialysate; C_P = concentration of solute in plasma; V_D = volume of dialysate effluent; T = dwell time of dialysate in the peritoneal cavity.

Peritoneal clearance is influenced by the volume and rate of dialysate exchanges, effective peritoneal membrane area, peritoneal blood flow, and transport characteristics of the peritoneal membrane. Peritoneal clearance is not constant during a dialysis exchange since the rate of diffusion peaks early during the exchange. However, during longer dwells of PD (≥ 4 hours) almost complete equilibration of small solutes occurs during the exchange. Thus, C_D and C_P equalize by the end of the exchange and essentially cancel each other in the above given formula. Therefore, clearance approximates the dialysate effluent volume per time, i.e., dialysate outflow volume including ultrafiltration. For example, a CAPD prescription of four 2-L exchanges per day with 2 L of daily UF would result in an estimated clearance of 10 L per day.

The selection of urea as the marker for adequate dialysis dose is still a controversial issue. Small solutes such as urea and creatinine (molecular weight 60 and 113, respectively) have been favored due to their rapid accumulation in blood when renal function diminishes and simplicity of their determination. While urea and creatinine both show a fair correlation between plasma concentrations and clinical outcome, data suggest that urea might be a better surrogate marker of uremic toxicity than creatinine.[62, 63] Nonetheless, it is well known that urea alone is not responsible for the uremic syndrome. The European Uremic Toxin (EUTox) Work Group has listed 90 compounds considered to be uremic toxins.[61] Sixty-eight have a molecular weight less than 500 Da, 12 exceed 12,000 Da, and 10 have a molecular weight between 500 and 12,000 Da. Twenty-five solutes (28%) are protein bound. It is important to keep in mind that the kinetics of urea removal are not representative of other molecules such as middle molecules or protein-bound solutes.

Solute removal by dialysis therapy is very limited when compared to the natural kidneys. Achieving appropriate small solute clearances as measured by the Kt/V_{urea} is only one part of adequate treatment. Other important factors are ultrafiltration volume, sodium intake and removal, maintaining normal hydration status and blood pressure, preservation of residual renal function and quality of life.

DIALYSIS PRESCRIPTION

To achieve adequate clearances, the appropriate dialysis modality and dose has to be prescribed. Apart from achieving the target clearances and the ultrafiltration necessary to maintain euvolemia, considering psychosocial implications of the chosen modality and patient preferences are equally important factors to consider.

The main determinants of dose as expressed in the Kt/V are clearance, time and urea distribution volume. The last two parameters are more or less fixed values, if we assume daily PD treatment and a stable V for each patient, depending on sex, age, height and weight. While V cannot be influenced significantly, a higher volume in larger patients still implies the need for higher clearances to achieve the same Kt/V than in smaller patients.

Clearance is highly dependent on the transport characteristics of the peritoneum known from the patient's PET. Shorter dwell times are required for high transporters and longer ones for slow transporters. Total daily dialysate drain volume directly determines solute removal. Thus, the clearance can be significantly improved by increasing dialysate flow through higher exchange volumes and more frequent exchanges. Additionally, UF contributes to the achieved drain volumes. Thus, higher glucose concentration impacts both UF and clearances. However, higher glucose concentration could potentially lead to more side effects and thus should be carefuly prescribed. The clearance of large molecules is mostly determined by the membrane permeability and the time of exposure of the dialysate to the peritoneal membrane, rather than by dialysate flow.

CAPD has been suggested for patients with residual renal function starting on dialysis.[85] As native renal function is lost, the dose must gradually be increased through more frequent exchanges or larger volume. In the absence of renal function, in large patients or fast transporters, CAPD might not provide sufficient clearance and water excretion to achieve adequate dialysis. These patients might benefit from APD as exchange volume and dwell time can be better optimized for achieving adequacy criteria.[86-88] Moreover, APD improves clearance by increasing effective surface area through the supine position of the patient.[56, 89-91] If needed, tidal dialysis or adding manual daytime exchanges, can further enhance peritoneal dialysis efficacy.

The selection of the most appropriate PD modality can be significantly simplified through the use of algorithms[92] or computer based kinetic modeling programs that help with the selection of optimal PD therapy including appropriate prescription.[93, 94] The use of an individualized, patient-tailored modality selection and prescription can support the patient's life style and ensure dialysis adequacy in the great majority of patients.[95]

COMPLICATIONS OF PERITONEAL DIALYSIS

Infections complications. Infections are the most important group of complications from PD. These include exit exit-site and tunnel infections, as well as peritonitis.

Peritonitis is an inflammation of the peritoneum, or abdominal cavity lining. It typically has an infectious etiology, mostly due to bacteria or, in rare cases, fungus. Peritonitis is a common complication of peritoneal dialysis, with approximately 4% of episodes resulting in death of the patient. However, recurrent peritonitis is associated with a higher mortality (16%). Peritonitis may be due to touch contamination during connection and disconnection (intraluminal), the consequence of exit-site infections (pericatheter or extraluminal), hematogenous, or from gynecological or intestinal sources as in the case of diverticulitis. Peritonitis often causes structural changes in the peritoneum that may be permanent and can result in membrane and technique failure. Peritonitis treatment goals include rapidly resolving inflammation by eradicating the causative organism(s) and preserving the function of the peritoneal membrane. Reductions in peritonitis rates have been observed with the introduction of better connectology, the use of Y-set CAPD systems and other "flush before fill" systems and the increased use of APD. Peritonitis and exit-site infections have been reported to account for 30-40% of transfers from CAPD to HD. A lower rate of peritonitis has recently been reported to have altered this trend.

Comprehensive best clinical practice guidelines were established for the diagnosis and treatment of peritonitis by the International Society of Peritoneal Dialysis in 2010.[69] Monitoring of peritoneal-dialysis infection (exit-site and peritonitis) rates and outcomes is key to quality assurance and improvement of any PD program. A goal rate of 1 episode per 18 months (0.67/year) is expected; although, rates of 1 episode per 41-52 months (0.29 - 0.23/year) are preferred. The purpose of evaluating the program's treatment regimen is to ensure best possible outcomes for patients. If the protocol is not effective in treatment and prevention of peritonitis, it should be reassessed and changes should be implemented to achieve satisfactory results.

The diagnosis of peritonitis is established by the presence of a cloudy dialysate with an effluent cell count greater than 100/μL white blood cells and at least 50% polymorphonuclear neutrophilic cells, after 2 hours of dwell time. The Gram stain should be used to define presence of yeast and permit initiation of antifungal therapy and timely removal of the catheter; however, the Gram stain has limited use for empiric therapy guidance. Sometimes the effluent may be clear despite abdominal pain. The differential diagnosis should include other causes aside from peritonitis, such as constipation, peptic ulcer disease, renal or biliary colic, acute intestinal perforation, and pancreatitis.

Obtaining the correct microbiological culture from the peritoneal effluent is necessary to identify the responsible organism, as well as the antibiotic sensitivities. After obtaining microbiological specimens for culturing, it is important to start the patient on two antibiotics, immediately one covering Gram-positive and one Gram-negative bacteria. Gram-positive antibiotic options include vancomycin or cephalosporins. Gram-negative coverage may be obtained through the use of aminoglycosides or third-generation cephalosporins (Table 2). The preferred administration of antibiotics is intraperitoneal; effective intermittent and continuous dosing regimens have been defined in the literature for most antibiotics (Table 3).

Subsequent to obtaining the results of the culture and sensitivities, it is recommended that the empiric antibiotic therapy be changed to a narrow-spectrum antibiotic to cover the specific organism as appropriate. Dose adjustments for drugs excreted by the kidney may be necessary in patients with considerable residual renal function. The clinical response is used to guide treatment and to determine the length of therapy. In general, clinical improvement should occur within the first 3 days after antibiotic initiation. In uncomplicated cases, a total of 14 days is usually prescribed, with the antibiotic being continued for 7 days after clearing of the effluent. A duration of 3 weeks may be necessary when patients are slower to respond to therapy, usually in the context of a severe infection often caused by Gram-negative organisms such as S. *aureus* or enterococci.

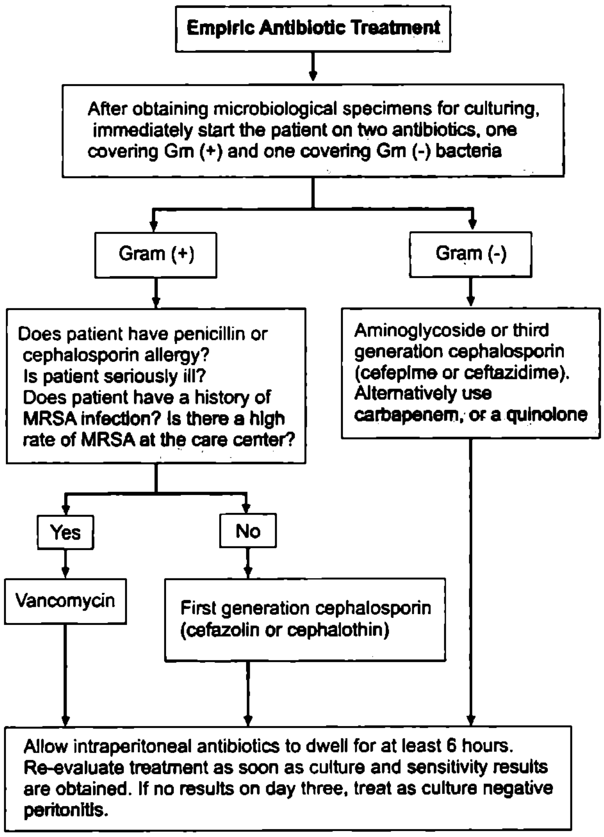
Removal of the peritoneal catheter should be considered in some cases in addition to antimicrobial treatment. Indications include refractory and relapsing peritonitis, refractory exit-site and tunnel infections, and fungal peritonitis. It may also be considered for repeat peritonitis, mycobacterial peritonitis, and multiple enteric organisms. In the case of relapsing peritonitis, once the effluent is cleared, the catheter can be removed and replaced in a single procedure with use of antibiotic coverage. It is recommended that a time period of 2-3 weeks be utilized between catheter removal and reinsertion when cases are refractory or fungal.

Each case of peritonitis should be evaluated to determine the cause of the peritonitis episode and the mitigation of potential risk factors to prevent future reinfection.

Exit-site infections of the peritoneal catheter are diagnosed by the presence of erythema, induration, tenderness and purulent discharge from the exit site.[27] Twardowski has classified healthy and abnormal

Table 2. Empiric peritonitis treatment

Empiric Antibiotic Treatment. Modified from: Li PK, Szeto CC, Piraino B, et al. Peritoneal dialysis-related infections recommendations: 2010 update. Perit Dial Int 2010;30:393-423.



Empiric Antibiotic Treatment

After obtaining microbiological specimens for culturing, immediately start the patient on two antibiotics, one covering Gm (+) and one covering Gm (-) bacteria

Gram (+)

Gram (-)

Does patient have penicillin or cephalosporin allergy?
Is patient seriously ill?
Does patient have a history of MRSA infection? Is there a high rate of MRSA at the care center?

Aminoglycoside or third generation cephalosporin (cefepime or ceftazidime). Alternatively use carbapenem, or a quinolone

Yes

No

Vancomycin

First generation cephalosporin (cefazolin or cephalothin)

Allow intraperitoneal antibiotics to dwell for at least 6 hours. Re-evaluate treatment as soon as culture and sensitivity results are obtained. If no results on day three, treat as culture negative peritonitis.

Table 3. Antibiotic dosing regimens

Antibiotic dosing regimens. Based on: Li PK, Szeto CC, Piraino B, et al. Peritoneal dialysis-related infections recommendations: 2010 update. Perit Dial Int 2010;30:393-423. [1] Dosing of renally eliminated drugs in patients with residual renal function (defined as >100 mL/day urine output), may be empirically increased by 25%; [2] Vancomycin should be re-dosed if serum trough levels fall below 15 μg/mL; [3] Given in conjunction with 500 mg quinupristin/dalfopristin intravenous twice daily. CAPD: continuous ambulatory peritoneal dialysis. LD: loading dose. MD: maintenance dose IP (intraperitoneal).

Medication	*CAPD IP Dosing*[1]		*Automated PD IP Dosing*
	Intermittent (per exchange, once daily)	*Continuous (mg/L, all exchanges)*	*Intermittent (per exchange, once daily)*
Aminoglycosides			
Amikacin	2 mg/kg	LD 25, MD 12	
Tobramycin	0.6 mg/kg	LD 8, MD 4	LD 1.5 mg/kg IP in long dwell, then 0.5 mg/kg IP daily in long dwell
Gentamicin, netilmicin	0.6 mg/kg	LD 8, MD 4	
Cephalosporins			
Cephalothin, cephradine	15 mg/kg	LD 500, MD 125	
Cefazolin	15 mg/kg	LD 500, MD 125	20 mg/kg IP in long day dwell
Cefepime	1000 mg	LD 500, MD 125	1 g IP in 1 exchange daily
Ceftazidime	1000-1500 mg	LD 500, MD 125	
Ceftizoxime	1000 mg	LD 250, MD 125	
Penicillins			
Amoxicillin	No data	LD 250-500, MD 50	
Ampicillin, oxacillin, nafcillin	No data	MD 125	
Azlocillin	No data	LD 500, MD 250	
Ampicillin/sulbactam	2 g every 12 hrs	LD 1000, MD 100	
Penicillin G	No data	LD 50000 units MD 25000 units	
Quinolones			
Ciprofloxacin	No data	LD 50, MD 25	
Others			
Aztreonam	No data	LD 1000, MD 250	
Daptomycin	No data	LD 100, MD 20	
Linezolid	Oral 200-300 mg daily		
Teicoplanin	15 mg/kg	LD 400, MD 20	
Vancomycin (Dose depends on serum trough levels)	15-30 mg/kg every 5-7 days[2]	LD 1000, MD 25	LD 30 mg/kg IP in long dwell; repeat dosing 15 mg/kg IP in long dwell every 3-5 days
Imipenem/cilastatin	1 g twice daily	LD 250, MD 50	
TMP/SMZ	Oral 960 mg BID		
Quinupristin/dalfopristin	25 mg/L in alternate bags[3]		
Antifungals			
Amphotericin B	Not applicable	1.5	
Fluconazole	200 mg IP every 24-48 hrs		200 mg IP in 1 exchange per day every 24-48 hours

catheter exit sites and has provided a pictorial reference catalog.[66, 67] The most common organisms are *Staphylococci*. While most Gram-positive bacterial infections are easily treated with systemic antibiotics, Gram-negative organisms may lead to chronic, often indolent, resistant infection requiring removal of the peritoneal catheter and temporary cessation of PD. Exit-site infections occur at a rate of approximately one to two episodes per year depending on catheter implantation technique, modality of treatment and trauma to the exit-site area. *S. aureus* nasal carriers are at particular risk of developing exit-site infections.[68]

Tunnel infections can be the consequence of extensions from an infectious process at the exit site or from peritonitis. They are often manifested by erythema, intense tenderness along the subcutaneous tunnel, fluctuance, and eventual drainage through the exit site or into the peritoneal cavity leading to peritonitis. The diagnosis is usually made on clinical grounds, although ultrasound of the anterior abdominal wall can be very helpful. Incision and drainage is imperative in order to control the infection. Removal of the catheter is often necessary with temporary cessation of PD and reinsertion of a new catheter once healing has occurred.

Non-infection complications are most commonly related to elevated intra-abdominal pressure, metabolic effects of glucose and peritoneal membrane failure.[76]

Intra-abdominal pressure-related complications. The instillation of PD solutions into the abdominal cavity necessarily results in increased intra-abdominal pressure (IAP).[70] This increase in IAP is greatly influenced by position.[71, 72] The usual volume of 2 L of dialysate in the average adult patient results in an abdominal pressure of <10 cm H_2O in the supine position and increases further with the patient standing and is even higher when the patient is sitting. IAP can be checked while the patient is lying down by measuring the height of the water column in the PD catheter from the mid anterior-posterior line of the body. It should never exceed 15 cm H_2O in supine position since higher pressure may lead to pericatheter leaks, hernia formation, gastroesophageal reflux, hydrothorax and scrotal or vulvar edema. The incidence of hernia has been reported to be as high as 24% among the CAPD population. Surgical repair is often required followed by a reduction in dialysate volume or transfer to APD with the use of higher volumes at night with the patient in the supine position and a reduction in volume during the day when IAP is likely to be higher.

Leaking of dialysate around the exit site or subcutaneous tunnel usually presents early in the course of PD before the catheter has completely healed.[28] The leak often stops after temporary cessation of PD and reinitiation with lower volumes of dialysate. On occasion, surgical intervention is required to minimize or eliminate the space between the catheter and the peritoneal cavity. Pleuroperitoneal communication should always be suspected when a patient on PD develops an unexplained pleural effusion which is usually right-sided. A definite diagnosis can be made using radioisotopic injection into the peritoneal space and scanning over the lung, or by sampling the pleural fluid with demonstration of a high glucose concentration. Although surgical correction may be required, this complication often presents an important contraindication for chronic use of PD. Development of scrotal or vulvar edema may be due to either dissection of fluid into the preperitoneal space or a patent processus vaginalis. The former usually subsides after temporary cessation of CAPD while the latter requires ligation of the processus vaginalis. The diagnosis can be established with the use of radioisotopic injection into the peritoneal cavity and scanning over the genital area or through CT scanning of the area after intraperitoneal injection of contrast material.

Metabolic complications The continuous absorption of glucose from the peritoneal cavity into the systemic circulation results in an increased caloric load, hyperinsulinemia and hyperglycemia in diabetic patients. Glucose absorption generally provides 200-700 kcal/day depending on the degree of peritoneal permeability, number of dialysis exchanges and glucose concentration of the dialysate. The increased glucose loads can result in obesity in some patients even though many of the patients are protein deficient. Another metabolic consequence of these glucose loads is hypertriglyceridemia. The increased caloric load in addition to protein losses, including lipoprotein, can also lead to more complex alterations in the lipid profile. Atherogenic lipid profiles (hypercholesterolemia, increase in low density lipoprotein and hypertriglyceridemia) have been observed among patients undergoing PD.[73] The ultimate clinical effects of these findings is not clear, but dietary intervention, modification of the dialysis prescription and pharmacologic manipulation of hyperlipidemia seem justified in light of our knowledge of abnormal lipid metabolism on cardiovascular system.

Malnutrition is another concern among long-term CAPD patients. Malnutrition is common with both HD and PD. However, the potential for induction or worsening of protein malnutrition through peritoneal protein losses is significant in PD. The association between serum albumin concentration and odds of death has been well documented for both HD and PD.[77-79] A low initial albumin has been shown to be a potent marker of clinical outcome among PD patients.[80,81]

Another group of patients that may be considered at high risk of developing malnutrition are those with high peritoneal transport rates. These patients are known to lose more protein in their PD effluent and are at higher risk than patients with lower transport rates.[82-84] If inadequate dialysis is the cause of protein malnutrition, it is imperative to select a modality capable of providing sufficient solute clearance.

Peritoneal membrane failure. Preservation of the anatomical and physiologic integrity of the peritoneal membrane is of utmost importance for the chronic delivery of PD. The majority of patients undergoing CAPD can maintain adequate solute transport and ultrafiltration for many years.[74] However, a small but clinically significant number of patients develop ultrafiltration failure or peritoneal sclerosis.

Ultrafiltration failure is characterized by a progressive increase in peritoneal permeability, resulting in rapid absorption of dialysate glucose, prompt blunting of the osmotic gradient between dialysate and plasma, as well as absorption of dialysate. Ultrafiltration failure may exist from the onset of peritoneal dialysis, but more often develops or progresses with time on PD. The precise etiology remains unclear and may be multifactorial. Glucose degradation products and hypertonicity in the dialysate, peritonitis, and dialysate contaminants have been suggested as potential etiologic agents. The diagnosis is supported by simple measurements of net ultrafiltration after a four-hour dwell with a 2.5% dextrose dialysis solution or more precisely using a standard PET. If the severity of ultrafiltration failure is mild, a switch to NIPD using shorter dwell times and frequent exchanges with solutions of higher osmolality can be attempted. Due to the increased rate of solute transport, adequate or comparable clearances can be maintained. However, because of the potential for further membrane deterioration, regular monitoring of peritoneal membrane function is recommended, preferably with serial PETs. Discontinuation of PD and transfer to HD may be necessary if more severe changes are observed.

An extremely serious complication of PD is peritoneal sclerosis. This condition is characterized by progressive thickening of the peritoneal membrane, development of thick adhesions between bowel loops and eventual envelopment of all intra-abdominal organs resulting in bowel obstruction, necrosis and death.[75] Peritoneal sclerosis leads to reduction or elimination of the free space within the abdominal cavity and gradual loss of peritoneal surface area. The etiology is probably similar to that of ultrafiltration failure. The diagnosis is best established with the use of PET or by abdominal scanning after injection of contrast material through the PD catheter. Peritoneal biopsy may determine the severity of sclerosis. When this diagnosis is suspected, discontinuation of PD is recommended.

CLINICAL OUTCOME

Total life expectancy of an individual with end stage renal disease (ESRD) is only one-fourth to one-fifth that of the general population.[96] This difference in survival can be attributed to the higher rates of cardiovascular and infectious complications associated with ESRD.[96] Despite these risks, the overall mortality rate of peritoneal dialysis (PD) and hemodialysis (HD) has considerably improved during the past two decades. Advancing technologies, earlier referral, and better management of comorbid disease states and infections have all positively impacted the mortality rate of the dialysis population. The rate of PD mortality has fallen more rapidly compared to HD due to major improvements in PD delivery, efficacy and safety.[96, 97] Furthermore, adjusted five-year survival on PD improved 7.5% between the 1992-1996 and 1997-2001 periods and is now similar between HD and PD patients at 33.5% and 33.9%, respectively, during the first three years of therapy.[96]

Although the adjusted survival of PD and HD over the total 5-year period is almost identical, the relative risk of death between the two modalities appears to change over time on dialysis. Several recent studies indicate that PD is associated with better survival during the first 1-2 years of dialysis, whereas HD is associated with better survival thereafter.[98-107] Several explanations for this shift have been proposed including: a reduced rate of loss of residual renal function in patients on PD; a greater level of comorbidity; the fact that a high rate of venous catheter use among HD patients at initiation[98] seems to benefit early PD survival, whereas technique failure due to recurrent peritonitis and loss of ultrafiltration[103] might become more relevant after the first few years on PD. Apart from general differences between treatment modalities, survival is also dependent on other patient specific factors such as age, gender, race, body weight, and educational status. Understanding these subgroup differences and mortality trends is essential for optimizing patient outcomes.

Due to the difference in early and late survival, between modalities some have suggested using a "dual-modality" or "integrative-care" approach with initiation of PD, followed by timely transfer to HD. A study by Van Biesen et al. showed a survival advantage in a matched-pair analysis of patients who started on PD and were transferred to HD, versus patients who started and remained on HD.[99] Similarly, a retrospective analysis of data from China on incident patients treated with either PD or HD also found that initial treatment with PD was associated with a better survival rate.[108] Yet, a study by Traynor et al. reported that initial dialysis modality was not a significant predictor of survival after adjusting for age, sex and primary renal diagnosis.[109] Thus, in the absence of randomized controlled studies, definitive recommendations regarding the dialysis modality based on mortality rates cannot be made.

In addition to general differences in outcome depending on treatment modality, individual patient outcome is determined by a set of patient characteristics that affect PD & HD mortality. Age, gender, ethnicity, race, body mass index, educational background, health literacy and the patient's comorbid conditions are patient-specific variables that will influence outcome on HD or PD treatment. Choosing the right patient for the right modality has been shown to have a great impact not only on health-related outcomes but also on quality of life.[110-115] Thus, it is important to consider the social implications of each modality on the patient's life. Independent from patient characteristics and preference, the quality of general and nephrological care will affect the outcomes of dialysis. Inadequate training of the clinician or patient will lead to high rates of technique failure and mortality.[116] Clinical knowledge and training has historically focused more on center HD than PD. Many nephrology training programs do not offer trainees sufficient exposure to home therapies. Accordingly, center experience has been shown to have a significant impact on the relative risk of death and technique failure in PD. Comparing centers with the most and the least cumulative experience with PD, patients treated at more experienced centers had a 30% reduction in risk of death. Risk of technique failure was also diminished by PD experience; 17% reduction for the most versus x% for the least experienced.[117] Clinician education has historically focused more on HD than PD.[118-120] However, this trend appears to be changing with the increasing focus on dual therapy and home therapies. Adequate training and education of patients and health care professionals, together with thoroughly considering the impact of patient characteristics and patient preference are the critical key to success in peritoneal dialysis.

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Immunologic Concepts of Renal Transplantation

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INTRODUCTION

Biology of transplantation is known since very early part of this century. Majority of renal transplantations are allotransplants. "Allo" relationship is a concept, which describes the relationship between two members of the same species who are not genetically identical. Thus we can have alloantigens, allografts, and alloantibody, etc. Before going into details of immunological concept, certain basics of proteins and its related structures must also be known for better understanding of immunological concepts.

PROTEIN AND RELATED SUBSTANCES

Proteins are important biological **macromolecules** present in all organisms. They are made up primarily from the elements carbon, hydrogen, nitrogen, oxygen, and sulphur. All proteins are **polymers** of amino acids, also known as a **polypeptide,** consists of a sequence of 20 different L-α-amino acids, also referred to as **residues.** For chains under 40 residues the term **peptide** is used instead of protein. To be able to perform their biological function, proteins fold into one or more specific spatial conformations, driven by a number of noncovalent interactions such as hydrogen bonding, ionic interactions, van der Waals forces, and hydrophobic packing. A certain number of residues is necessary to perform a particular biochemical function, and around 40 to 50 residues appears to be the lower limit for a functional **domain** size. However, the estimate for the average protein length is around 300 residues. Very large aggregates can be formed from protein subunits. Proteins have got many grades of structures.

Primary Structure

Primary structure is the amino acid sequence of the peptide chains.

Secondary Structure

It is highly regular sub-structures (***alpha helix*** and *strands* ***of beta pleated sheet***).The **alpha helix (α-helix)** is a right-handed coiled or spiral conformation, in which every backbone N-H group donates a hydrogen bond to the backbone C=O group of the amino acid four residues earlier. This secondary structure is also sometimes called a classic **Pauling-Corey-Branson** alpha helix. Among types of local structure in proteins, the α-helix is the most regular, predictable and prevalent form.

Tertiary Structure

It is three-dimensional structure of a single protein molecule; a spatial arrangement of the secondary structures. It also describes the completely folded and compacted polypeptide chain.

Quaternary Structure

It is a complex of several protein molecules or polypeptide chains, usually called **protein subunits** in this context, which function as part of the larger assembly or protein complex.

Further, in addition to four levels of structure, a protein may shift between several similar structures in performing its biological function. This process is also reversible. In the context of these functional rearrangements, these tertiary or quaternary structures are usually referred to as chemical conformation, and transitions between them are called conformational changes.

Domains, Folds, and Motifs of Protein Structure

A structural **domain** is an element of the proteins that is self-stabilizing and often folds independently of the rest of the protein chain. Many domains, name and structure are not unique to a particular protein product of one gene or one gene family but can appear in a variety of proteins. Domains often are named because they figure prominently in the biological function of the protein to which they belong; for example, the "calcium-binding domain of calmodulin." Because they are self-stabilizing, domains can be "swapped" by genetic engineering between two proteins. A **motif** refers to a small specific combination of secondary structural elements (such as helix-turn-helix). These elements are often called **super secondary structures**. Structure motifs usually consist of just a few elements, e.g., the "helix-turn-helix" has just three. Protein structural motifs often include loops of variable length and unspecified structure, which in effect create the "slack" necessary to bring together in space two elements that are not encoded by immediately adjacent DNA sequences in a gene. Fold refers to a global type of arrangement, like helix bundle or beta-barrel. Despite the fact that there are about 100,000 different proteins expressed in eukaryotic systems, there are much fewer different domains, structural motifs and folds. This is partly a consequence of evolution, since genes or parts of genes can be doubled or moved around within the genome. This means that, for example, a protein domain might be moved from one protein to another thus giving the protein a new function. Because of these mechanisms, pathways and mechanisms tend to be reused in several different proteins.

IMMUNOGLOBULINS

Immunoglobulins (Ig) are components of immunoglobulins super family proteins which have one or more Ig domains (Fig. 1). The Ig domain is a polypeptide of about 90 amino acids typically encoded by one exon (an exon is a nucleic acid sequence that is represented in the mature form of an RNA molecule). It contains seven β strands, designated A-G, separated by six "loops" 1 to 6. The β strands align to form two antiparallel β pleated sheets, one four-stranded (A, B, E, D) and one three-stranded (C, F, G), connected by a disulfide bond. The β strands confer the structure and the loops mediate many of the functions, especially loops 2, 3 and 6. They also have other domains, including membrane anchors; intracytoplasmic domains which may have signaling functions; and "sheet and helix" domains, as seen in the MHC proteins. All of them have in common that their basic unit is formed by two pairs of peptide chains: a pair of Light chains or L chains (approximately 220 amino acids each) and a pair of Heavy chains or H chains (around 440 amino acids each). These four chains in the basic structure are linked through disulfide bridges between cysteine residues in the backbone of the peptide chains. Each Light chain is linked to one Heavy chain and each Heavy chain is associated to a Light chain and to the other Heavy chain. Light chains can be distinguished into two regions or domains: VL (variable L) and CL (Constant L), while in the H chains, 4 regions or domains can be found: VH, CH1, CH2 and CH3. Each of these regions is composed by 70 to 110 amino acids. The V regions are variable regions: the amino acid sequence in these regions (the NH2- terminal regions) is highly variable, and within them, in the L and in the C chains, there are hypervariable regions (CDRs of Complementarily determining regions) that form the specific antigen binding site complementary to the specific antigen.

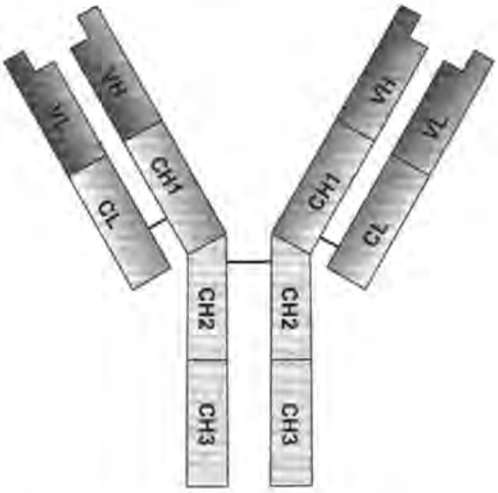


Figure 1: Immunoglobulin basic structure showing light and heavy chain along with its constant (CH) and variable (VH) region.

THE MAJOR HISTOCOMPATIBILITY COMPLEX

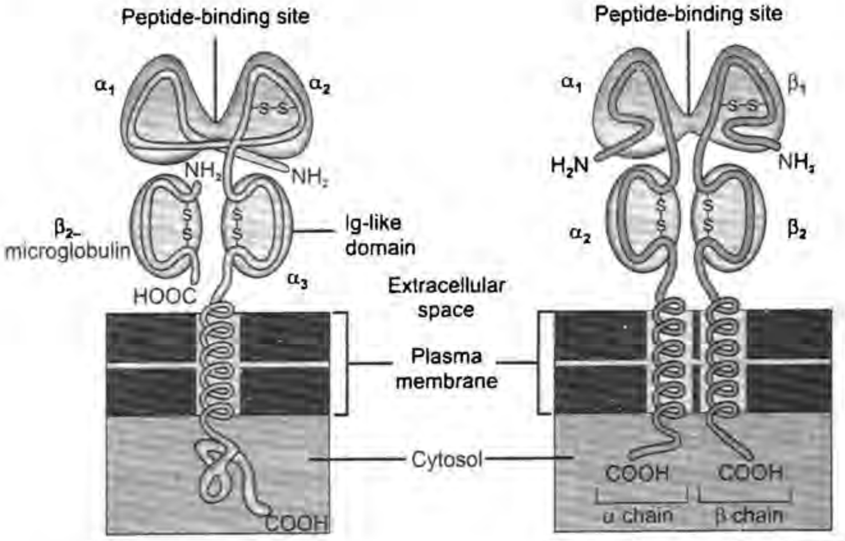
As defined earlier, an alloantigen is an antigen that is a part of an ***animal's self-recognition system,*** Major histocompatibility complex (MHC) molecules. When enters into another animal, they trigger an immune response aimed at eliminating them. Therefore, it can be thought of as an antigen that is present in some members of the same species, but is not common to all members of that species. If an alloantigen is presented to a member of the same species that does not have same alloantigen, it will be recognized as foreign and body will react to destroy it. Thus, it will be necessary at this stage to understand MHC molecules. The human MHC is the human leukocyte antigen (HLA) complex of genes. It has four million base pairs (bp) on the short arm of chromosome 6 (6p). These genes encode the most strong transplantation antigens, the class I and II MHC proteins.

The MHC Proteins

The MHC class I and II proteins are antigen presenting structures (Fig. 2). They bind peptides inside cells and display them on the cell surface for T cells to "read". They also play a role in the ontogeny of T cells in the thymus. Class I is expressed on most cells while class II has a restricted tissue distribution, confined to specialized antigen presenting cells (APCs) like macrophages and B cells. Class II samples the peptides in the endosomal compartment of antigen presenting cells, looking for proteins taken up by endocytosis, e.g., from extracellular agents.

MICA and Kidney Transplant

Major-histocompatibility-complex (MHC) class I-related chain A (MICA) antigens are surface glycoprotein with functions related to innate immunity. MICA antigens are expressed on endothelial cells, dendritic cells, fibroblasts, epithelial cells, and many tumors, but not on peripheral-blood lymphocytes. As with the HLA antigens, which resemble MICA antigens only remotely in terms of structure, exposure to allogenic MICA during transplantation can elicit antibody formation. Since MICA antigens are not expressed on lymphocytes, the types of cells commonly used for cross-matching, antibodies directed against MICA are not detected with the methods generally used. However, polymorphic MICA antigens are expressed on endothelial cells and have been found to be cytotoxic in the presence of serum complement. Thus such antibodies are likely to be harmful to vascularized organ allografts. However, their role in clinical kidney transplant is yet to be determined.



(A) class I MHC protein

(B) class II MHC protein

Figure 2: Basic structure of major histocompatibility complex (MHC) molecules showing class I and class-II molecules. (For detail see text)

B-CELL RECEPTOR AND ANTIBODY

B lymphocytes and their progeny, plasma cells, make immunoglobulin. Immunoglobulin can serve as the antigen receptor or can be released into the circulation. Each clone of B cells expresses only one type of light chain (lambda or kappa) with one type of VL region. It can make only VH, but can associate this with different CH and thus switch the class of Ig which it is making. Switching CH while retaining the same VH and L chain is called *Ig class switching*. Since the clone makes only one VL and one VH, it can make only one antigen specificity. The B cell antigen receptor on naive B cells is monomeric IgM. Some B cells also have IgD receptors. After antigen exposure they undergo class switching and express IgG, IgA, or IgE on their membranes. Stimulation of the cell results in massive production of soluble antibody.

T-CELL RECEPTOR (TCR)

The structure of TCR is very similar to Fab fragment of immunoglobulin, which are regions defined as the combined light and heavy chain of an antibody (Fig. 3). The TCR is a dimer of nonidentical α and β chains. Each chain of the TCR is a member of the immunoglobulin superfamily and possesses one N-terminal immunoglobulin variable (V) domain, one Ig-constant (C) domain, a transmembrane/cell membrane-spanning region, and a short cytoplasmic tail at the C-terminal end. The variable domains of both the TCR α-chain and β-chain have three hypervariable or complementary determining regions. The variable region of the β-chain has an additional area of hypervariability (HV4) that does not normally contact antigen and therefore is not considered a complementary determining region.

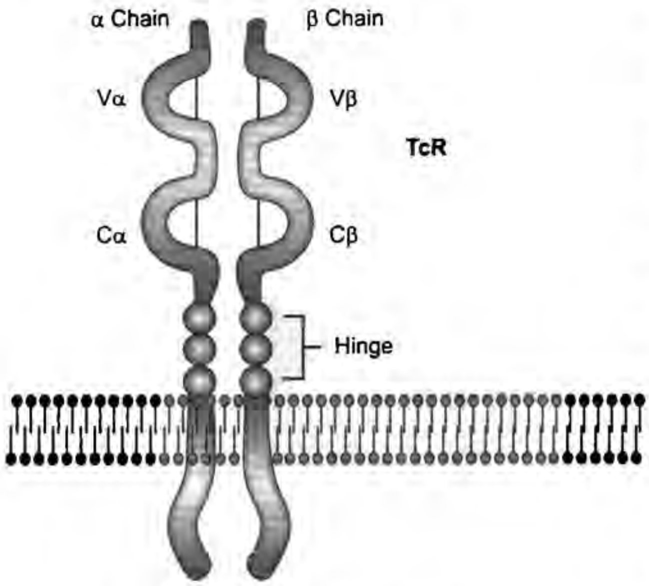


Figure 3: Basic structure of T-cell receptor

The peptides are located in two regions of the TCR, at the interface of the α- and β-chains and in the β-chain framework region that is thought to be in proximity to the CD3 signal-transduction complex. complementary determining region-3 is the main CDR responsible for recognizing processed antigen, although CDR1 of the alpha chain has also been shown to interact with the N-terminal part of the antigenic peptide, whereas CDR1 of the β-chain interacts with the C-terminal part of the peptide. CDR2 is thought to recognize the MHC. CDR4 of the β-chain is not thought to participate in antigen recognition, but has been shown to interact with super antigens. There is another TC receptor, which is a dimer of γ and δ chains, but most allorecognition can be attributed to α β receptors. The γ δ receptors are similar to α β receptors.

Mechanism of Engagement of MHC and TCR

It is likely that all six CDRs (3 at α and 3 at β) of the TCR engage the upper surface of the MHC. The outer regions of the TCR (CDRs 1 and 2) engage the α-helices of the MHC, and the central region (the CDR3s) engages the peptide. One model is that the TCR-α chain CDRs engages the α-helix of the α1 domain of class I or class II. The TCR-β chain engages the other α-helix—either the α2 domain of class I or the β1 domain of class II. The CDR3 region is the most variable of the CDRs in the T-cell receptor. The CDR3s have to bind to the antigenic peptide, whereas the CDR1 and 2 must engage the α-helices, which are much less variable.

CD4, CD8 and CD3

CD4 and CD8 are termed co-receptors because they bind to the same MHC molecule as does the TCR, and are often important for TCR triggering. The CD4 molecule is a chain of four Ig domains, a membrane anchor and an intracellular portion. The CD4 first and second domains form a rigid rod because the last β strand of the first domain (strand G) is elongated to become the first β strand of the second domain. The N terminal domain is of the V type. The third and fourth domains repeat this arrangement to give a second rod, hinged to the first. The two N terminal domains engage the β chain of MHC class II. The CD4-class II β2 domain interaction may be species specific. The CD8 molecule is a dimer, similar to TCR. The CDR loops of the V domains of CD8 engage the class I MHC molecule in the α3 domain. CD8 may be either an αβ or αα dimer; the functions of these dimers may differ. The CD8-class I interaction is species specific, which could be relevant in xenotransplants.

The **CD3** molecule (Fig. 4) is associated with TCR and CD-3:T Cell co-receptor is a protein complex and is composed of four distinct chains. It contains a CD3 γ chain, a CD3 δ chain, and two CD3ε chains. These chains associate with a TCR and the ζ-chain to generate an activation signal in T lymphocytes. The TCR, ζ-chain and CD3 molecules together comprise the TCR complex. The CD3γ, CD3δ, and CD3ε chains are related cell surface proteins of the immunoglobulin super family containing a single extracellular immunoglobulin domain.

The transmembrane region of the CD3 chains is negatively charged, a characteristic that allows these chains to associate with the positively charged TCR chains. The intracellular tails of the CD3 molecules contain a single conserved motif known as an *immunoreceptor tyrosine-based activation motif* (ITAM), which is essential for the signaling capacity of the TCR. Phosphorylation of the ITAM on CD3 renders the CD3 chain capable of binding to an enzyme called ZAP70 (zeta associated protein), a kinase that is important in the signaling cascade of the T cell.

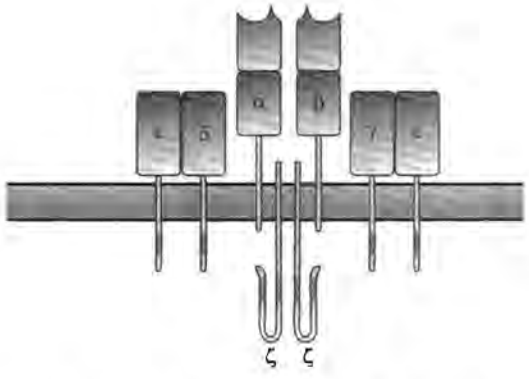


Figure 4: Schematic structure of CD3 molecule complex

Allorecognition: Direct and Indirect

When T cells of a recipient encounter allogenic MHC, along with appropriate additional signals, stimulation of some of the recipient T-cell clones occurs. Small numbers of amino acid differences in the donor MHC can lead to strong responses. This could be because either they alter groove shape and thus determine peptide occupation of the groove or they change the shape of the upper surface of the native molecule and change the interaction with the TCR or they make MHC peptides antigenic. The donor MHC differences can be presented by either a direct or indirect pathway of presentation. ***"Direct"*** refers to recipient T cells recognizing donor MHC molecules on donor antigen presenting cells. Direct recognition could reflect recognition of α-helix differences affecting the contact sites for TCRs on the α-helices; or differences in the peptides in the groove. ***"Indirect"*** presentation of donor MHC requires recipient antigen presenting cells with peptides of donor MHC molecules in their grooves. Indirect pathway is important since immunity and tolerance can be induced by peptide alone. Peptides from MHC class I proteins are prominent among peptides occupying the class I groove and peptides of class I and II and invariant chain are prominent in the class II groove of DR1. This has given rise to the possibility that a major component of across an MHC difference is due to recognition of MHC peptides in the donor (direct) or host (indirect) MHC grooves. Indirect presentation of allogeneic donor MHC peptides in self MHC class II grooves (and possibly in class I grooves) by host antigen presenting cell (APC) must involve recognition of differences in amino acid sequences. Indirect presentation is a distinct possibility for triggering CD4 T cells, and could generate "help" for both T cell and antibody responses as well as inflammation akin to "delayed type hypersensitivity". However, graft injury by cytotoxic T cells must involve direct recognition.

T-CELL TRIGGERING

Nature of TCR Triggering

The sufficient binding of TCRs to MHC molecules is the first step in T cell activation following exposure to antigen. The signal requires the CD3 complex. CD3 is altered following TCR binding to MHC by one of two mechanisms: engagement of the V regions alters remote parts of the TCR, which in turn alters the CD3 complex or cross-linking. Combination of two class II molecules also brings TCRs together to aid triggering. This means that class II recognition proceeds through a complex of two TCRs and two CD4. Class I may be able to form multimers and the dimeric nature of CD8 and of class II suggest that cross-linking could occur. Further, TCR-mediated T cell activation in vivo may reflect molecular changes triggered by the assembly of the TCR CD3-CD4 or CD8 complex, in which the CD4 or CD8 molecules play key roles. The CD3 complex acts as transducer and informs the interior of the cell that the TCR has engaged MHC. The ζ chains interact directly with the tyrosine kinases. Meanwhile CD4 (or CD8) engage the MHC, and assembly of the complex brings a series of tyrosine kinases together.

Role of Tyrosine Kinases (TK)

The CD3-TCR complex is associated with at least three TKs: ZAP, p59fyn, and p50csk. CD4 and CD8 are associated with another protein tyrosine kinase, p56lck. Tyrosine kinases phosphorylate the tyrosine peptides in the CD3 molecule ζchain. The function of p59fyn is important for TCR signaling and p56lck is important for thymocyte development. The p50csk is involved in negative signaling (tolerizing) the T cell when the TCR is signaled. TKs activate many following signaling pathways.

1. Ras: The tyrosine kinases can activate the Ras pathway and then trigger a cascade which can activate enzymes such as mitogen activated protein kinase (MAP kinase) and eventually impact on cell division.
2. PLC-γ1: This lyses the membrane phospholipid phosphatidyl inositol bisphosphate to yield inositol trisphosphate (IP3) and diacylglycerol (DAG). DAG activates protein kinase C (PKC) and IP3 binds to receptors on the endoplasmic reticulum to release stored calcium and raise intracytosolic calcium levels.
3. Phosphatidyl inositol-3-kinase

Further, each of these pathways has multiple consequences leading to expression of many genes, blast transformation, mitosis and expression of effector functions. The calcium-dependent pathway is critical for T-cell activation and important in transplantation. High intracellular calcium activates calcium-regulated enzymes, particularly the enzyme calcineurin (CN). This is a calcium- and calmodulin dependent serine phosphatase. It activates transcription factors for some key cytokines, particular members of the nuclear "factor of activated T cells" or NF•AT family. Calcineurin is the target for some of the most important immunosuppressive agents, cyclosporine and tacrolimus as a group called calcineurin inhibitors.

Co-stimulation (Signal-2)

When the naive T cell is exposed to alloantigen, other than MHC and TCR interaction, which is called signal-1, it requires other signals for activation, what is called classic two-signal model of lymphocyte activation (Fig. 5). "Signal 2" is the nonantigen signal provided by antigen presenting cells. When T cells engage antigen without appropriate second signals, anergy is the result. This makes the identity of the second signals crucial for transplantation and immunosuppression. If we could block second signal, we might induce anergy and tolerance. Signal-2 involves certain adhesion molecules of the immunoglobulin super family, notably B7-1 and B7-2 (also called B70) on the APC, engaging CD28 on the T cells. CD28 amplifies and prolongs signal 1, increasing IL-2 transcription and prolonging the half life of IL-2 mRNA. One of the key sites for regulating signal 2 is an expression of CD40 ligand.

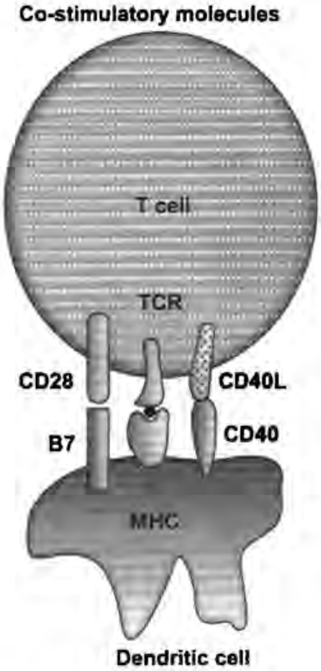


Figure 5: Schematic representation of co-stimulatory molecules

Intracellular Signaling

PLC-γ1, activated by tyrosine phosphorylation, lyses membrane phosphatidyl inositol bisphosphate (PIP2), releasing diacylglycerol (DAG) and inositol trisphosphate (IP3). DAG activates PKC which is also activated through other pathways, including calcium flux. PKC activation leads to the transcription of several genes which encode transcription factors such as *fos* and *jun* which form the complex called AP-1, composed of the Jun and Fos proteins.

IP3 binds to receptors on the endoplasmic reticulum which causes sustainable release of calcium into the cytosol. The high calcium activates calcium-dependent enzymes, one of which is calcineurin (CN). Calcineurin activates cytosolic factors called NF-AT, which is free to translocate from the cytosol to the nucleus. The ultimate result is a wave of transcription of cytokine mRNAs. This is the "second wave" of protein synthesis, the first being the nuclear factors which control the cytokine promoters. In this sense the cytokines are "early" genes. Naive CD4 T cells make *predominantly IL-2* in their first encounter with antigen, whereas previously stimulated or memory T cells make other cytokines also. The cell becomes committed to activation, differentiation, mitosis, and clonal expansion. Effector functions result like cytotoxicity in CD8 cells. In the end, molecules associated with memory and recirculation, such as the "very late antigens" or VLA molecules appear.

Cytokines and their Role

The term "cytokine" is group of substances which includes the interleukins, interferon, and colony stimulating factors of the hematopoietic and host defense system. They are protein mediators which signal cells through specific membrane receptors. Most of the cytokines have certain common characteristics:

1. Short half-life for fine regulation.
2. Relatively small size: the typical cytokine gene is about 4 to 5 kb in length
3. α-helical structure: usually four to six α-helices, sometimes with very short β strands
4. Commonly Multimers: IFN-γ and TGF-β are dimers, and TNF-α is a trimer
5. Cytokines are synthesized and secreted when needed and are not stored
6. They are usually not expressed as membrane proteins with few exceptions
7. The main control of cytokine production is transcriptional
8. Usually act in concert with other cytokines interactions like synergy, competition, and antagonism
9. Cytokines are pleiotropic (i.e., have many effects) and redundant (i.e., have overlapping effects)
10. Cytokines commonly induce other cytokines in a cascade
11. Cytokines often have self-amplifying circuits to facilitate rapid potent responses
12. The potency of the cytokine response is impressive
13. Most cytokines affect in inflammation and host response to injury or infection
14. "Knockout mice" are providing important insights into the roles of cytokines and their receptors
15. *Cytokine receptors* are typically multimers of different transmembrane proteins which have an external ligand-binding domain, and an intracytoplasmic signaling domain
16. One or more chains may bind the cytokine with high affinity, but the multimers is required for internalization and/or signaling
17. Cytokine receptors are classified into families on the basis of their external, ligand binding domain. Some important cytokine receptors are:
    - The hemopoietins, e.g., IL-2R β-chain
    - The interferon and IL-10 receptors, e.g., IFN-γR
    - The TNF receptor
    - IL-8 and its relatives

Binding of the cytokine to the receptor alters the cytoplasmic domain of the receptor and triggers second messengers usually through a kinase (usually tyrosine kinase or less commonly a serine/threonine kinase). PTKs activate PLC-γ, PI-3 kinase and other second messengers with downstream activation of serine-threonine kinases, e.g., PKC and release of intracellular calcium. The final effect is often on transcription factors, but there are other events also like direct effects on membrane receptors or cytoplasmic effector mechanisms. Signal transduction, through the IFN-γ receptor, is a useful example of a cytokine system which we can watch in operation in transplant rejection. IFN-γ engages the IFN-γR and activates two tyrosine kinases, JAK1 and JAK2, which phosphorylate a factor called STAT. This induces transcription of selected genes by moving to the nucleus and engaging specific sites in their promoters. Several cytokine receptors, including

IL-2R, apparently utilize a signal transduction pathway which involves the activation and phosphorylation of an enzyme called the "Target of Rapamycin" or TOR. TOR in turn activates p70 S6 kinase. The role of TOR kinase is probably crucial in the initiation of cell division by cytokines. TOR acts to increase the translation of existing mRNAs for proteins which control the cell cycle.

The Chemokines

Chemokines are recently described cytokines, 8 to 10 kD in size, with activity in inflammation and tissue repair. Its members include:

1. IL-8
2. Groα
3. Monocyte chemotactic protein (MCP)
4. RANTES

All the chemokines have cysteine residues which form disulfide bridges. Chemokines play a key role in inflammation and immune responses by their chemotactic activities and their ability to attract and activate neutrophils, monocytes, T cells, eosinophils and basophils. Antigen specific T cells activated by APC express new chemokine receptors. This antigen-activated T cell now migrates to inflammatory site in response to chemokines released in the inflamed site. T-cell infiltration into the affected area involves a process of endothelial adhesion followed by release of T cells, followed by adherence to extracellular matrix via integrin molecules. IL-8 and Gro-α are chemoattractant for neutrophils and contribute to extravasation of neutrophils. Neutrophils can produce several polypeptides mediators of inflammation, including IL-1, IL-6, IL-8 and TNF. At the site of injury neutrophils promote tissue damage by release of lysosomal enzymes and superoxide anions. Organ preservation as well as immune activity could be improved through manipulation of chemokines.

SPECIFIC IMMUNE RESPONSES OF T CELLS AND B CELLS

Activated CD4 cells influence other cells either by the production of cytokines or interaction through their receptors to signal the target cell, and direct interaction through their TCRs and adhesion and signaling molecules. Direct interactions must involve the same MHC plus peptide for which the CD4 T cell is primed. In direct interactions, the release of cytokines is directional, focused on the target by the TCR and the adhesion molecules. Activated CD4 cells do three major functions:

1. It helps CD8 cells to become cytotoxic.
2. It helps B cells to make antibody.
3. It helps to activate macrophages and endothelial cells to mediate delayed type hypersensitivity.

TH1 and TH2 Paradigm

The primary function of CD4 T cells is to produce cytokines, which they do more efficiently than CD8 cells. Naive CD4 T cells produce primarily IL-2. With prolonged stimulation CD4 T cells stops production of some cytokines and increase production of others in characteristic patterns called a "TH1" pattern or "TH2" pattern. The TH1 pattern of cytokine production is

- IFN-γ
- Lymphotoxin
- IL-2.

The TH2 pattern consists of—

- IL-4
- IL-5
- IL-6
- IL-10

No cytokine constitutes an exclusive marker for any CD4 phenotype: for example, IL-10 can be produced by CD4+ TH2 cells and also by many TH1 cells and non T cells. IFN-γ is a "TH1 cytokine", but most of it is made by other T cells (CD8 T cells and CD4 T cells not fitting the TH1 definition) or by NK cells. It is better to reserve the term TH1 and TH2 "subsets" *for circumstances.* Under most circumstances, TH1 and TH2 cytokines are *not* made by CD4 T cells which fulfill the criteria for TH1 and TH2 subsets.

TH2 cytokines particularly IL-4 and IL-5 are important in activation of resting B cells to proliferate and differentiate. In addition, IL-10 enhances viability of B cells and upregulates MHC class II expression on resting B cells. TH1 cytokines are important mediators of delayed type hypersensitivity (DTH). **TH1 cytokines** can enhance or suppress B cell responses, depending upon the relative amounts of IL-2 and IFN-γ. IL-2 in large amounts enhances differentiation, proliferation, and Ig production. IFN-γ in low concentrations enhances certain antibody responses but in high amounts suppresses both proliferation and Ig secretion and can be cytotoxic to activated B cells. TH2 cytokines also favor IgE and IgG1 responses. The generation of CD8+ cytotoxic T cells is enhanced by both TH1 and TH2 cytokines. IL-2, IFN-γ, IL-4, and IL-5 all enhance the generation of cytotoxic T cells although IL-2 is most effective.

Importance of "Suppressor" T Cells

All cytokines have both positive and negative effects, and the cells which produce them cannot be assigned a uniquely positive or negative function except in relationship to one specific set of circumstances and one specific target system. TH2 cytokines such as IL-4 can suppress DTH responses but stimulate IgE responses. Thus T cells producing IL-4 can have many simultaneous functions, positive and negative, depending on where the IL-4 is received. So suppression by IL-4 is really a characteristic of the cell that receives IL-4, not the cell that produces it. Similarly, cells producing TGF-β are negative regulators in some types of inflammation and positive in others. In clinical transplantation, where negative regulation is vital to success, the agenda has shifted from suppressor T cells to a detailed analysis of the role of particular molecules in negative regulation of graft injury and inflammation, such as TH2 cytokines and TGF-β rather than suppressor cell itself.

THE ADHESION MOLECULES

Adhesion molecules are involved in all levels of the immune response and inflammation and are classified into three groups: the Ig super family; the integrins; and the selectins. Selectins are named for the cells that express them. E (endothelial)- selectin, is induced by IL-1 and TNF. Its ligand is L(leukocyte)-selectin, which is important for both endothelial binding during inflammation and as a recirculation receptor. L-selectin also binds to P (platelet)-selectin, which is stored in granules of platelets and endothelial cells and is released in response to clotting cascade products. The leukocyte interacts with endothelium through interactions between the selectins. The result is loose binding permitting the leukocyte to roll along the endothelium. This permits the integrins and Ig super family members to interact, which causes tight binding and flattening. This will occur only in areas where the endothelium has been activated by injury, infection or immune activity to increase the expression and activity of the adhesion molecules.

ENDOTHELIAL CELLS

Endothelial cells are no more just a lining but can act as antigen presenting cells and can respond to many stimuli. EC respond to cytokines in following ways:

1. Induction of MHC class II and class I expression.
2. Increase in the expression and functions of many adhesion molecules.
3. Generalized activation and even proliferation.
4. Promoting hemostasis by promoting thrombosis and fibrin formation through synthesis of thromboplastin and suppression of thrombomodulin/protein C. Further, platelet activating factor (PAF) has been demonstrated in the EC plasma membranes and may act locally on adhering leukocytes.
5. Regulation of vascular tone through local release of endothelin (vasoconstrictor) and nitric oxide (NO), an endothelium-derived relaxing factor, vasodilator prostacyclin (PGI2) or the vasoconstrictor thromboxane. Balance between vasoconstrictor and vasodilators forces contributes to the complex vasomotor changes such as arterial vasoconstriction.
6. Change in vascular permeability through intermediate actions on neutrophils, and could thus play a role in the edema characteristic of acute rejection.
7. EC also respond to the inflammatory cytokines IL-1 and TNF by producing other soluble factors like IL-1α (provide co-stimulation to bound T cells), IL-6, PAF and various chemokines.

IFN-γ PRODUCTION AND REGULATION

Interferon-gamma (IFN-γ) is a dimerized soluble cytokine that is the only member of the type II class of interferons. This interferon was originally called macrophage-activating factor, a term now used to describe a larger family of proteins to which IFN-γ belongs. In humans, the IFN-γ protein is encoded by the *IFN-γ* gene. IFN-γ is produced by T cells (CD4, CD8) and NK cells. It is critical for innate and adaptive immunity. The importance of IFN-γ in the immune system stems in part from its ability to inhibit viral replication directly, but it derives from its immunostimulatory and immunomodulatory effects. IFN-γ production is an important event in rejection, with both adverse and favorable effects. IFN-γ mediated MHC induction is probably necessary but not sufficient for rejection. IFN-γ is produced by the specifically triggered T cells and is also capable of triggering its own release, probably from NK cells. Two IFN-γ receptors bind the IFN-γ homodimer, each engaging the N terminal of one unit and the C terminal of the other. Receptor cross-linking leads to membrane-to-cytoplasm signal transduction via mechanisms involving the large intracytoplasmic domain of the receptor. The mechanism involves a protein kinase and the receptor becomes phosphorylated. One tyrosine in the intracytoplasmic portion of the receptor has been shown to be essential to the biological activity of the receptor. The receptor has additional subunits, encoded on chromosome 21 and chromosome 16 in the human. Tyrosine kinases (JAK1 and JAK2) then phosphorylate the cytoplasmic form of a transcription factor, interferon stimulated gene factor 3, in particular, the p91 component, now called STAT-1. This then moves into the nucleus to activate transcription of genes with IFN-γ activated sites. Some of these induced mRNAs encode products are transcription factors. MHC expression is induced later than many other genes after IFN-γ administration. It is possible that MHC induction requires the synthesis of IFN-induced transcription factors such as IRF-1.

TARGET INJURY

The hallmark of acute T-cell mediated rejection is injury to the endothelial and parenchymal cells, initially reversible, but eventually becoming irreversible. Inflammation is probably necessary but not sufficient for rejection injury. The parenchymal injury is usually conceptualized as apoptosis of individual parenchymal cells triggered by cytotoxic T cells. Many cytokines such as TNF-α are expressed in rejecting or inflamed grafts, but no single cytokine has been shown to mediate rejection injury.

Role of Antibodies in Allorejection

Antibody plays a major role in acute transplant rejection, especially in the increasing population of recipients sensitized to MHC antigens. Endothelial cells are important targets for antibody. The sequence of events in antibody-mediated rejection seems to involve endothelial dysfunction and injury, via complement and neutrophils, followed by vasospasm, ischemic injury, fibrin and/or platelet deposition, and infarction or hemorrhage. Another area where antibodies are very important is hyperacute rejection. It is mediated by preformed antibodies against HLA class I molecules or by antibodies such as ABO blood group antigens. A population of antibodies against poorly defined endothelial antigens of arteries ("anti-endothelial antibodies") also mediates hyperacute and accelerated rejection. Anti-class II antibodies rarely mediate hyperacute rejection. A positive B-cell cross match is frequently due to antibodies which are not class II specific. Antibodies against B cells are often autoantibodies. Low levels of anti-class I can also produce a positive B-cell cross match with a negative T cell cross match because B cells are relatively rich in class I.

OUTCOME OF ALLOGRAFT

Once an allograft is transplanted, it can be rejected or it can be adapted by the recipient. Rejection can also be acute or chronic. Acute type of rejections can also be hyperacute, accelerated or acute.

REJECTION

Hyperacute Rejection

If a kidney is transplanted into a recipient who has high levels of preformed antibodies against donor alloantigens of the graft endothelium, particularly HLA class I or ABO blood group antigens, *hyperacute rejection* follows. The antibodies on the endothelium fix complement, which attracts polymorphs, and destroy the endothelium within hours or even minutes. Hyperacute rejection is usually prevented by "crossmatching", i.e., testing the recipient's serum for complement-dependent antibodies against donor lymphocytes.

Accelerated Rejection

If the recipient has previously been sensitized against donor antigen by previous pregnancies, transfusions, or previous grafts, but does not have preformed antibodies in the circulation, rejection may occur around day two or three, earlier than typical acute rejection. This *accelerated rejection* is more vigorous and is a reflection of specific immunologic memory for the antigens of the graft. It is mediated by the rapid return of high levels of specific T cells and/or alloantibody directed against the antigens of the graft.

Acute Rejection

Around five to seven days following renal transplantation, the tissue begins to manifest signs of two processes: inflammation and specific cell injury. The inflammation is manifested by infiltration with mononuclear cells, accompanied by edema and reduced blood flow; specific destruction of parenchymal and endothelial cells by infiltrating lymphocytes, coupled with decreased perfusion, cause a rapid loss of function. This can cause acute rejection. It is donor cell injury which defines rejection. Thus tubulitis in kidney transplants constitute rejection. In general, areas of high MHC class I and II expression, either basal or inducible, are important targets of acute rejection.

Tubulitis in renal transplants refers to invasion by lymphocytes which cross the basement membrane and attack the basolateral membrane of the epithelial cells, where MHC products are expressed. The lymphocytes are believed to be T cells expressing cytotoxic molecules, but more details on the cells in these lesions are needed. The endothelium of small arteries and arterioles in graft is damaged in the lesion known as intimal arteritis or endothelitis. Lymphocytes adhere to the endothelium, infiltrate beneath it and lift up the endothelial cells. The result is increased resistance, perhaps due to loss of endothelial regulation of vasomotion, increased coagulation, and eventual loss of perfusion and downstream ischemia. Lymphocytes infiltrate through the basement membrane and recognize alloantigens expressed on the MHC of graft epithelial cells and mediate cell death via apoptosis or cell lysis.

The mediators of cell injury include cytokines, Fas and granule contents (serine esterases and perforins), both concentrated on the target cell by receptor directed exocytosis, and in some cases cytotoxic alloantibody. Serine esterases are expressed in the infiltrate of rejecting grafts. Numerous cytokines are found in the infiltrate of rejecting grafts or in the serum. Some may cause injury, but some may reflect the response to injured tissue. Both CD4 and CD8 T cells are present in rejection and neither has an exclusive role. There are nonspecific as well as alloantigen-specific lymphocytes in the cellular infiltrate. Macrophages are abundant within rejecting grafts and may play a role in the immune injury. Macrophages make a wealth of cytokines, growth factors, eicosanoids, enzymes, procoagulant activities, NO, etc. and may contribute to the parenchymal and endothelial cell injury and dysfunction in vascularized grafts. But the majority of early injury is probably due to specific T cells.

Chronic Rejection

An initially successful transplant may gradually lose its function in a slow scarring process. The arteries become obstructed by intimal thickening, and the graft undergoes progressive parenchymal atrophy and interstitial fibrosis. Some cases have proteinuria and a variable glomerular lesion termed "transplant glomerulopathy". Hypertension is frequent. *Chronic rejection* has been most studied in patients with renal transplants, and can occur months to years after transplantation. In some cases it may be antibody-mediated also. Chronic rejection often follows acute rejection, and some observers believe that acute rejection, which is incompletely reversed, is the harbinger of chronic rejection. Despite its nonspecific features, chronic rejection may result from a specific immune response. The immune mechanisms appear to be additive with other factors related to the age, acute injury, hypertension, etc. The final common pathway may have elements in common with other chronic diseases or aging.

GRAFT ADAPTATION

Once an allograft is transplanted, alloantigen can result in a positive response or a negative response ("tolerance"), or no response ("neglect"), depending on the circumstances in which the antigen is presented. Tolerance is defined as a state of antigen-specific unresponsiveness induced by exposure to antigen. The ability to induce tolerance is vital for self and nonself discrimination. Tolerance is classified by location: central versus peripheral. The principal mechanism of *central tolerance* in the thymus during T-cell ontogeny is clonal deletion by apoptosis. Intrathymic injections of antigen can induce tolerance. Central tolerance is believed to have little role in transplantation although microchimerism with donor cells could play a role centrally. In general, chimerism can induce tolerance only in significant levels, and microchimerism does not correlate with true tolerance. Successful transplantation involves a degree of peripheral tolerance. There are several possible mechanisms.

1. *Clonal expansion followed by clonal deletion.* This is particularly true for responses to "superantigens", which delete previously expanded clones as an

outcome of powerful immune responses probably by programmed cell death. Lack of co-stimulatory signals (IL-1, adhesion molecules) may promote peripheral clonal deletion.

2. *Clonal anergy means nonresponsiveness without deletion* is demonstrable in some circumstances. It is dependent on the continuous presence of Ag and the lack of IL-2. Exogenous IL-2 reverses the state of anergy. Some patients receiving long-term immunosuppression with functioning allografts simulate this state.
3. Low T cell reactivity to MHC class II a form of "neglect".
4. Cytokines of the TH2 type, e.g., IL-10, may suppress IL-2 and IFN-γ expression but it is difficult to imagine long-term high levels of cytokine production as a mechanism for maintaining tolerance. Clinical immunosuppressive treatment, particularly with cyclosporine and steroid may also act in this way, selectively reducing IL-2 and IFN-γ production.
5. Down-regulation of TCRs and co-receptors (CD4 or CD8).
6. "Veto cells" (these are T cells which inactivate T cells which try to recognize them).
7. Anti-idiotypes, which are antibodies directed against idiotypes, an antigen combining sites, either of TCRs or antibodies.

Adaptive Changes in Graft

Following transplantation, if the graft survives, with time the inflammation subsides, and the induced expression of adhesion molecules and MHC antigens in the graft returns toward normal. There is a progressive loss of the donor antigen presenting cells, replaced by the recipient cells. Thus both direct antigen presentation by donor cells and indirect presentation by host cells subside. However, any injury, including ischemic and reperfusion injury, rejection, and viral infection, can promote inflammatory changes and sustain the immune process. The changes of inflammation and those of tissue repair in response to injury overlap.

Microchimerism

The transfer of tissue from a donor to a recipient transfers some bone marrow-derived cells, some of which are stem cells. The donor bone marrow-derived cells can persist and establish bone marrow *microchimerism*, which means permanent persistence of small numbers of bone marrow derived stem cells of donor type, presumably due to establishment of a few donor stem cells. This would link transplantation- induced peripheral tolerance, which is probably a chimeric state. Some long-term transplant recipients have evidence of microchimerism, even decades after the transplant. Persistent donor cells could be the result or the cause of host hyporesponsiveness. Microchimerism in long-term survivors could lead to central tolerance and clonal deletion by colonization of the host thymus by donor stem cells. Implantation of allogeneic tissues in the thymus before allografting is an strategy for inducing some central tolerance.

DRUG MODIFICATION OF IMMUNE RESPONSE

A considerable success of renal transplant is because of effect of immunosuppressive medication used in these patients. This therapy is utilized for induction, maintenance and rejection phases. The term "maintenance immunosuppression" is usually used to describe drug regimens administered to stable kidney transplant recipients. The main objective of maintenance immunosuppression in kidney transplant recipients is to prevent allograft failure while maintaining kidney function, minimizing adverse effects of immunosuppressive drugs, and preserving immune homeostasis such that defense against microbes and malignant cells remain intact. The commonly used drugs for maintenance immunosuppressive therapy include are corticosteroids, calcineurin inhibitors (CNIs; cyclosporine and tacrolimus), antiproliferative agents (mycophenolate mofetil [MMF], and its sodium compound and Azathioprin) and inhibitors of the mammalian target of Rapamycin (sirolimus and everolimus). At discharge from the hospital following kidney transplantation, tacrolimus is the CNI of choice, used in 72 percent of patients and MMF is the most frequently used antiproliferative agent used in 81 percent of patients.

Calcineurin Inhibitors

Cyclosporine and tacrolimus are fungus-derived small molecules that are the mainstays of current maintenance immunosuppressive regimens. These drugs inhibit antigen-specific signaling. CNIs bind to cytoplasmic proteins called immunophilins (cyclosporine binds to cyclophilin and tacrolimus binds to FK-binding protein). The immunophilin-drug complex then inhibits the activity of calcineurin, a serine phosphatase that normally dephosphorylates nuclear factor of activated T cells resulting in nuclear translocation of the factor and transcription of interleukin-2. Interleukin-2 has an important role in activation and proliferation of T-lymphocytes. CNIs, therefore, are potent anti-T-cell agents. Furthermore, the pharmacokinetic profiles of CNIs vary depending on patient age, gastrointestinal milieu, ethnicity and comorbidities, and drug formulation. As such, careful monitoring (at least monthly) of drug blood levels is necessary. Studies that compared outcomes of tacrolimus-based versus cyclosporine-based immunosuppression in kidney transplant recipients detected no difference in rates of early or late graft or patient survival, despite lower rates of acute rejection among tacrolimus-treated patients. These drugs can induce acute renal failure in the absence of permanent structural injury through hemodynamic changes resulting from afferent arteriole vasoconstriction, or kidney allograft injury secondary to thrombotic microangiopathy. CNIs also cause a chronic form of allograft injury, characterized by progressive and irreversible interstitial fibrosis and arteriolar hyaline changes. The toxicity of these drugs has spurred attempts at CNI avoidance, withdrawal or minimization. These protocols should only be implemented in selected patients and in collaboration with transplant centers.

Antiproliferative Agents

Antiproliferative agents inhibit the proliferation of activated immune cells by interfering with different aspects of either DNA or RNA synthesis. Azathioprine and prodrugs of mycophenolic acid (MPA; MMF and MPS) function primarily as inhibitors of purine synthesis, whereas leflunomide is an inhibitor of *de novo* pyrimidine production.

AZATHIOPRINE

Metabolism of azathioprine releases 6-mercaptopurine, which blocks *de novo* and salvage pathways of purine synthesis and inhibits DNA replication. The use of azathioprine as a maintenance immunosuppressant in kidney transplant recipients has currently decreased to nearly 4 to 5 percent only. The main adverse effects of azathioprine are bone marrow suppression, lymphomas and skin cancers.

PRODRUGS OF MYCOPHENOLIC ACID (MPA)

MPA—the metabolite of both MMF and enteric-coated MPS—is a noncompetitive and selective inhibitor of inosine monophosphate dehydrogenase, the rate-limiting enzyme of the *de novo* pathway of purine synthesis. Inhibition of this enzyme prevents proliferation of activated T cells and B cells. When administered orally or intravenously, virtually 100 percent of MMF is converted to the pharmacologically active MPA in the intestinal wall, blood and liver within 30 min. MMF accounts for 82 percent of the antiproliferative prescriptions among kidney transplant recipients. Enteric-coated MPS was developed in an effort to overcome the gastrointestinal toxicity of MMF; however, its utility in this regard has been questioned. The prodrugs of MPA are relatively safe immunosuppressive agents that have similar adverse-effect profiles. MPA trough levels can be checked in the event of unexplained diarrhea, leukopenia, anemia, BK virus infection or late cytomegalovirus infections.

LEFLUNOMIDE

Leflunomide—a synthetic organic isoxazole derivative—and its analog FK778 are antiproliferative drugs that inhibit the activity of dihydroorotate dehydrogenase, a rate-limiting enzyme of *de novo* pyrimidine biosynthesis. Inhibition of dihydroorotate dehydrogenase prevents lymphocytes from accumulating sufficient pyrimidines to support DNA synthesis. Although not yet approved by the FDA for kidney transplantation, this drug has been used successfully in kidney transplant recipients with chronic kidney allograft dysfunction, polyoma virus nephropathy, and cytomegalovirus infections. Gastrointestinal adverse effects, bone marrow suppression and severe hepatitis can occur with the use of leflunomide.

Inhibitors of the Mammalian Target of Rapamycin

Sirolimus and its derivative everolimus are macrolide immunosuppressant isolated from *Streptomyces hygroscopicus*. Sirolimus and Everolimus bind to the same immunophilin that is complexed by tacrolimus (FK-binding protein 12 [FKBP12]). Sirolimus—FKBP12 and everolimus—FKBP12 complexes inhibit mammalian target of Rapamycin, resulting in the inhibition of lymphocyte proliferation and cell cycle arrest in G1 phase. Oral bioavailability is poor (10 to 16 percent) with significant interindividual and intraindividual differences, and half-life is prolonged (approximately 63 h). The 2-hydroxyethyl chain substitution at position 40 of the Everolimus molecule improves mildly its oral bioavailability (approximately 16 percent) and reduces its tissue distribution, half-life (28 h) and time needed to reach steady-state concentrations, compared with sirolimus. Sirolimus can be useful in CNI minimization and/or withdrawal strategies in select patient populations. Sirolimus has notable adverse effects including bone marrow suppression and hyperlipidemia, and might be associated with reduced allograft survival in patients receiving full-dose CNIs, and in those with decreased kidney function and proteinuria.

Corticosteroids

Corticosteroids have been a cornerstone of transplant immunosuppression for the past 50 years. Due to interest in corticosteroid-sparing strategies, 30 to 40 percent of kidney transplant recipients currently discharged from hospital are not taking prednisone. Corticosteroids modulate genes involved in priming the innate immune response (i.e., cell-adhesion molecules, chemokines, and cytokines). They also suppress cellular (T_H1) immunity and promote humoral (T_H2) immunity. Corticosteroids have good oral bioavailability (60 to 100 percent), are eliminated by hepatic conjugation, and are excreted by the kidney as inactive metabolites.

CONCLUSION

The success of a kidney transplant is a function of several variables including technical, preservation and drugs to prevent and treat rejection. However, the magnitude of the immunological response against the graft is the key determinant of acceptance or nonacceptance of a technically perfect graft. The likelihood of acceptance or rejection is closely related to the extent of genetic differences between the donor and recipient of the graft. In recent years enormous progress has been made in the study of the MHC, yet we still know very little about the products of the numerous minor histocompatibility antigens. New insights into basic immunologic issues will likely have important consequences for clinical transplantation in the future.

KEY POINTS

1. Primary, secondary, tertiary, and quaternary structure of proteins, made up of carbon, hydrogen, nitrogen, oxygen, and sulphur are important biological macromolecules present in all organisms. They are also basic structure of immunoglobulin formed by two pairs of light chains and a pair of heavy chains. Both have constant and variable region with different functions.
2. The major histocompatibility complex (MHC) is self-recognition system having class I and II proteins with differential expression in body. Following exposure to antigen, a series of events develop leading to body immune reaction against the antigen, involving B cells and plasma cells for antibody mediated events and T-cells and cytokines for cell mediated events.
3. T-cell receptor like immunoglobulin is a dimer of nonidentical α and β chains with variable, constant, transmembrane and a cytoplasmic component. It along with CD3 and CD4 molecules, also called co-receptors is important for engagement of the MHC.
4. Allorecognition can be "direct," which refers to recipient T cells recognizing donor MHC molecules on donor antigen presenting cells or "indirect," which refers to presentation with peptides of donor MHC molecules in the grooves of recipient antigen presenting cells. Along with T-cell receptor binding to MHC, called signal-1, a second signal (co-stimulation), a nonantigen signal provided by antigen presenting cells is also required for appropriate allostimulation. This leads to intracellular signaling and release of various cytokines leading to alloantigen destruction by antibodies and cell mediated immune destruction. Depending upon the pattern of cytokines production, "TH1" pattern or "TH2" pattern, response may differ.
5. Endothelial cells are no more just a lining but can act as antigen presenting cells and can respond to many stimuli.
6. Once an allograft is transplanted, alloantigen can result in a positive response or a negative response ("tolerance") or no response ("neglect"), depending on the circumstances in which the antigen is presented. As per timing and mechanisms, graft rejection is of hyperacute, accelerated, acute, and chronic type. Their presentation and treatment is different and their response to therapy is variable. Successful transplantation involves a degree of peripheral tolerance.

7. Various types of drugs called immunosuppressive are available which can suppress the immune injury and prevent the graft damage. Major types are calcineurin inhibitors, anti-metabolites, steroid, M-Tor inhibitors and monoclonal and T-cell depleting antibodies. Usually they are given in combination rather than alone. Combinations are little different at initial period as compared to long-term period following transplantations. Depending upon their potency, cost, side effects, various combinations are in use with successful outcome of transplantation.

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Diagnosis and Management of Post-transplant Medical and Surgical Complications

Vinay Malhotra, Pankaj Beniwal

Renal transplantation is the best form of renal replacement therapy for patients with end-stage renal disease (ESRD) as it is associated with higher patient survivals, lower hospitalization rates and a superior quality of life. Advances in immunosuppressive therapy and refinement in surgical techniques have led to excellent short-term and long-term survival amongst renal allograft recipients. Traditionally, the post-transplant period has been staged as early (first three months) and late. Relatively high levels of immunosuppressants are used in the early period post-transplant and also most acute complications (medical and surgical) occur during this period. The diagnosis and management of post-transplant medical (excluding rejection) and surgical complications described below would be discussed in this chapter:

- Surgical complications
- Gastrointestinal complications
- Infectious complications
- Metabolic complications
- Hematologic complications
- Hypertension
- Bone disease
- Oncologic complications

SURGICAL COMPLICATIONS

The overall incidence of surgical complications after kidney transplant is low with most centers reporting an incidence of 5 to 10 percent. The clinical presentation of surgical and nonsurgical complications of kidney transplantation may be similar. The fundamental algorithm in the management of post-transplantation graft dysfunction requires that vascular and urologic causes of graft dysfunction be ruled out before concluding that an event is a result of a medical cause such as rejection or cyclosporine toxicity. Early diagnosis and appropriate intervention are crucial to minimize the detrimental impact on the graft and on the recipient. The important surgical complications after renal transplantation are summarized in Table 1.

Hemorrhage

Bleeding is uncommon after kidney transplants; it usually occurs from unligated vessels in the graft hilum or from small severed retroperitoneal vessels of the recipient. Risk factors include recipient obesity, antiplatelet agents, and anticoagulation. A falling hematocrit level, hypotension or tachycardia, and flank or lower quadrant pain should all raise concern regarding the possibility of bleeding. If a drain is present, it may provide visible evidence of bleeding. Administration of blood, efficient dialysis, estrogen infusions, and vasopressin may help in avoiding surgical exploration. Ultrasound can help to confirm and monitor a perigraft hematoma. If more than four units of blood are required within 48 hours, operative evacuation of the hematoma will usually accelerate graft function and patient comfort. Late profound hemorrhage can result from the rupture of a mycotic aneurysm. Nephrectomy and repair of the artery are usually required.

VASCULAR COMPLICATIONS

Vascular complications can involve the donor vessels (renal artery thrombosis, renal vein thrombosis),

Table 1. Important surgical complications after kidney transplants

Cause	*Characteristics*	*Diagnosis*	*Treatment*
Renal vein thrombosis	Sudden drop in urine output Dark hematuria Tender, swollen graft	Ultrasound with Doppler	Reexploration for thrombectomy or nephrectomy
Renal artery thrombosis	Sudden drop in urine output Usually no tenderness over graft	Ultrasound with Doppler	Reexploration, usually for nephrectomy
Ureter obstruction	Elevated creatinine	Hydroureter (per ultrasound) Possible lymphoceles (per ultrasound)	Percutaneous nephrostogram Drainage of any lymphoceles
Urine leak	Fever, pain over graft Fluid leak from wound	Fluid analysis for creatinine (high if urine leak)	Percutaneous nephrostomy and stenting of ureter Surgical reexploration for early leak or unsuccessful medical treatment
Wound infection	Erythema around wound Drainage from wound	Physical examination Ultrasound or CT (to rule out deep infection)	Wound opening (for superficial infection) Drainage (for deep infection with fluid collection)

the recipient vessels (iliac artery thrombosis, pseudoaneurysms, deep venous thrombosis (DVT)), or both. Depending on the vessel involved, the result may be loss of the graft or even a lower limb.

Renal Artery Thrombosis

This complication usually occurs early after transplant; it is an uncommon event, with an incidence of less than 1 percent. However, it is a devastating complication, usually resulting in graft loss. Typically, it occurs within the first two to three days after transplantation secondary to a technical problem, such as intimal dissection or kinking or torsion of the vessels. Risk factors include hypotension, multiple renal arteries, and unidentified intimal flaps. Other causes include hyperacute rejection, unresponsive acute rejection, and a hypercoagulable state. Renal artery thrombosis presents with a sudden cessation of urine output. Diagnosis is easily made with color flow Doppler studies. Urgent thrombectomy is indicated, but the transplanted kidney has no collateral vessels, and its tolerance of warm ischemia is very poor. Therefore most of these grafts cannot be salvaged and require removal.

Renal Vein Thrombosis

Renal vein thrombosis typically occurs in the early postoperative period (first 10 days) and may result from angulation or kinking of the vein, compression by hematomas or lymphoceles, anastomotic stenosis, extension of an underlying DVT, and a hypercoaguable state. Patients may present with a tender swollen graft and hematuria. Doppler studies are again the best diagnostic tool. Urgent thrombectomy is indicated, but for most patients, graft salvage is not possible, so graft nephrectomy is usually required.

Venous Thromboembolism

Venous thromboembolic complications that affect the recipient vessels (DVT and pulmonary embolism) are not uncommon. The incidence of DVT is close to 5 percent; the incidence of pulmonary embolism is 1 percent. Risk factors include recipient age greater than 40 years, diabetes, thrombophilic disorders, and a history of DVT. Ultrasonic imaging is highly sensitive and specific in detecting proximal DVTs but far less satisfactory in detecting distal thrombi because of poor visualization of the calf veins. Patients with DVTs should receive anticoagulation therapy for at least three months. Prevention of venous thrombosis in transplant recipients should include intermittent pneumatic compression stockings that are fitted appropriately as well as early ambulation. The addition of 5000 U of unfractionated heparin subcutaneously is appropriate in high-risk recipients; however, there is a substantial risk for hemorrhagic complications in patients with renal insufficiency, and therefore no more than twice-daily dosing is advisable perioperatively. Outpatient therapy with low-molecular-weight heparin is unsuitable for renal transplant recipients because the degree of anticoagulation may be unpredictable and difficult to monitor.

Renal Artery Stenosis

Transplant renal artery stenosis (TRAS) has been reported to occur in 1 percent to 23 percent of recipients depending on the definition and diagnostic techniques used. Imaging with angiography remains the gold standard; however, it is often suspected on ultrasonography because administration of contrast is not recommended in patients with marginal renal function. A peak systolic velocity greater than 250 cm per second and a "tardus-parvus" arterial waveform are both suspicious for TRAS. The common causes of TRAS are summarized in Table 2.

If stenosis is suspected in the first postoperative month, then surgical revision of the anastomoses is usually the best option. Graft loss after surgical repair has been reported in up to 30 percent of cases and is a reflection of the difficulty in directly approaching the vascular anastomosis in a noncollateralized kidney. Beyond one month, percutaneous transluminal angioplasty is usually favored. The term pseudorenal artery stenosis has been used to describe the situation that can occur if an atherosclerotic plaque in the iliac vessels impairs blood flow to the transplant renal artery.

UROLOGIC COMPLICATIONS

Urinary tract complications, manifesting as leakage or obstruction, generally occur in 2 to 10 percent of kidney recipients. The cause is often ischemia of the transplant ureter. Rarely, life-threatening urinary tract complications can result in significant morbidity and graft damage.

Table 2. Potential causes of renal artery stenosis

Atherosclerosis of the recipient vessel
Acute or hyperacute rejection
Clamp injury to the recipient or donor vascular endothelium
Perfusion pump cannulation injury of the donor vessel
Faulty suture technique
Kinking and angulation

Urine Leaks

Leakage of urine most commonly occurs early in post-transplant period. It usually is a result of distal ureteric ischemia because the allograft ureter receives blood supply solely from the renal artery. Therefore, the preservation of a lower pole donor renal artery is essential to ensure the viability of the ureter. Causes other than ischemia include undue tension created by a short ureter and direct surgical trauma to the ureter (usually at the time of procurement). Presentation is usually before the fifth post-transplant week; symptoms include fever, pain, swelling at the graft site, increased creatinine level, decreased urine output, and cutaneous urinary drainage. Diagnosis is suggested by a significantly elevated creatinine of the fluid drained from the incision when compared with the plasma and is typically confirmed by cystogram, nuclear medicine scan or antegrade nephrostogram. Early surgical exploration with ureteral reimplantation is indicated for very early leaks, large leaks, or leaks that do not respond to conservative measures. Many leaks, however, may be managed by using the principles of drainage and stenting. Drain placement to evacuate a urinoma and urinary tract stenting (usually by percutaneous nephrostomy and stent placement) can successfully manage many urine leaks post transplant.

Urinary Tract Obstruction

Ureteral obstruction may present early or late. Early obstruction may be due to edema, blood clots, hematoma, and kinking. Late obstruction is generally due to fibrosis from chronic ischemia. Presentation is usually with an elevated serum creatinine level, which must be differentiated from other surgical and nonsurgical causes of increased creatinine. An ultrasound of the graft, assessing for hydronephrosis, is a good screening tool. A furosemide renogram is useful in less obvious cases of obstruction. A percutaneous nephrostogram is the most specific test. Initial treatment with percutaneous transluminal dilatation, followed by internal or external stent placement, has yielded good results. If such treatment is not successful, then surgical intervention is indicated. For very distal strictures, the transplanted ureter may be reimplanted into the bladder. If the stricture is more proximal, then the native ureter can be used to bypass the obstruction.

HEMATURIA

Mild hematuria is not infrequent. It is usually observed in the first 12 to 24 hours after transplant. In most patients, it resolves spontaneously. More extensive bleeding may result in retained blood clots and urinary tract obstruction, which is the most common cause of sudden cessation of urine output immediately after transplant. Continuous bladder irrigation will usually restore diuresis, but if not, cystoscopy may be necessary to evacuate the clot and cauterize the source of the bleeding, which is usually from the anastomotic site or the distal tip of the transplanted ureter.

Lymphocele

Lymphoceles are collections of lymph caused by leakage from severed lymphatics surrounding the iliac vessels or the renal hilum of the donor kidney. The larger the lymphocele, the more likely it is to cause pain, ureteral obstruction, or venous compression. Small lymphocele are usually asymptomatic. Lymphoceles have been reported to occur in 0.6 to 18 percent of cases. Incidence of lymphoceles can be reduced by minimizing the pelvic dissection, ligating lymphatics, and avoiding sirolimus in the early postoperative period. Additionally, placing an intraoperative drain and leaving it for the initial postoperative course has been shown to reduce lymphatic collections.

An ultrasound examination will confirm a fluid collection, but percutaneous aspiration may be necessary to rule out other complications such as urinoma, hematoma, or abscess. The fluid obtained from a lymphocele is clear and has high protein content, and the creatinine concentration is equal to that of serum.

No therapy is necessary for the common, small, asymptomatic lymphocele. The most common indication for treatment is ureteral obstruction. Symptomatic lymphoceles require drainage, which can be achieved either by surgery or by percutaneous radiologic methods. The standard surgical treatment is creation of a peritoneal window to allow for drainage of the lymphatic fluid into the peritoneal cavity, where it can be absorbed. Either a laparoscopic or an open approach can be used. Another option is percutaneous insertion of a drainage catheter, with or without sclerotherapy.

GASTROINTESTINAL COMPLICATIONS

Kidney recipients may develop surgical complications that are not directly related to the transplant surgery, but that affect other organ systems, most commonly the gastrointestinal (GI) system. The incidence of all GI complications is 5 to 25 percent. In the upper GI tract, the most common problem is peptic ulcer disease, with its associated complications such as bleeding and perforation. However, with the routine use of H 2 blockers and potent antacids, peptic ulcer disease has decreased considerably.

The most common lower GI tract complications post-transplant that may require surgical intervention are colon perforation and hemorrhage. Transplant recipients tend to develop constipation owing to inactivity, dehydration, electrolyte abnormalities, diabetes, and narcotic analgesia. Ogilvie syndrome (colonic pseudo-obstruction) is suggested by pancolonic dilation ≥10 cm in the absence of an obstructive lesion. Perforation can be due to diverticulitis, ischemic colitis, fecal impaction, and less commonly, undetermined forms of colitis. Emergent laparotomy is indicated in patients showing signs of peritonitis or clinical deterioration. The overall mortality rate for perforated colon in this immunosuppressed population is as high as 60 percent.

INFECTIOUS COMPLICATIONS

Kidney transplantation is associated with lower risk for infection than other solid organ transplantations, reflecting the elective nature of kidney transplantation and clinical and nutritional status of recipients. Infection however, remains a significant cause of morbidity and mortality in renal transplant recipients.

The risk of infection is a function of the net state of immunodeficiency and it changes over time, particularly with modifications in immunosuppression. Patterns of opportunistic infections after transplantation have been altered by routine antimicrobial prophylaxis for *Pneumocystis carinii* (also called *P. jirovecii*) and cytomegalovirus. Most infections occur in the first month after transplantation and are typically related to technical complications of the surgery or invasive medical devices and most commonly involve the genitourinary infection.

During months one to six, infections associated with postoperative complications or with enhanced immunosuppression can develop, persist, or recur (see Table 3). Augmented immunosuppression and use of lymphocyte depletion antibody treatment is associated with an increased risk for infection with immunomodulating viruses that enhance susceptibility to opportunistic infections by altering the expression of inflammatory mediators and cytokines by a complex interrelated cascade. CMV and other Human Herpes Viruses (HHVs) also exert an immunomodulating effect that has been implicated in allograft rejection, obliterative transplant arteriopathy, and post-transplantation lymphoproliferative disorder (PTLD). Infections in patients with long-term successful allografts and minimal immunosupression are typically similar to those that develop in persons in the community.

COMMON INFECTIONS POST TRANSPLANT

Urinary Tract Infections

Urinary tract infections (UTIs) are the most common bacterial infections following transplantation, with an incidence ranging from 35 to 79 percent. Genitourinary tract manipulation during transplantation, urinary catheters, anatomic abnormalities (e.g., ureterovesicular stenosis, ureteral stricture, vesicoureteric reflux), and neurogenic bladder also predispose to post-transplantation UTI. Treatment is important in order to avoid pyelonephritis. Typical pathogens include *Escherichia coli, Klebsiella, Proteus, Enterococcus, Enterobacter, Staphylococcus*, and *Pseudomonas*. In the case of recurrent infections, abscesses or other nidi of infection should be sought out by means of imaging with ultrasound or computed tomography. Early catheter removal decreases the incidence of UTI in renal allograft recipients. In addition, routine antimicrobial prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX), usually for six months after transplantation, has substantially reduced the incidence of UTIs to less than 10 percent and virtually has eliminated secondary bacteremia, unless urine flow is obstructed. Patients who are allergic to TMP-SMX can be treated with an oral quinolone.

A clean-catch midstream urine specimen should be submitted for quantitative bacterial and fungal

Table 3. Time of presentation of common infections post-transplant

< 1 Month	*1- 6 Months*	*> 6 Months*
Infection with antimicrobial resistant	With PCP and antiviral (CMV, HBV)	Community-acquired pneumonia,
species:	prophylaxis:	UTI
MRSA	Polyomavirus BK infection, nephropathy	Infection with aspergillus, atypical
VRE	*Clostridium difficile* colitis	molds, mucor species
Candida species (non-albicans)	HCV infection	Infection with nocardia, rhodococcus species
Aspiration	Adenovirus infection, influenza	Late viral infections:
Catheter infection	*Cryptococcus neoformans* infection	CMV infection (colitis and
Wound infection	Mycobacterium tuberculosis infection	retinitis)
Anastomotic leaks and ischemia	Anastomotic complications	Hepatitis (HBV, HCV)
Clostridium difficile colitis	**Without prophylaxis:**	HSV encephalitis
Donor-derived infection	Pneumocystis	Community-acquired (SARS,
(uncommon):	Infection with herpesviruses (HSV,	West Nile virus infection)
HSV, LCMV, rhabdovirus	VZV, CMV, EBV)	JC polyomavirus infection (PML)
(rabies), West Nile virus,	HBV infection	Skin cancer, lymphoma (PTLD)
HIV,	Infection with *Listeria, Nocardia, Toxoplasma,*	
Recipient-derived infection	*Strongyloides, Leishmania,*	
(colonization):	*Trypanosoma cruzi*	
Aspergillus, pseudomonas		

culture. Infection may be more difficult to eradicate associated with ureteral stents that can lead to formation of biofilm. If possible, the stent should be removed and the tip sent for culture. Antibiotic therapy should be tailored according to the offending microorganism and drug susceptibility tests. Antibiotic therapy is usually recommended for two to three weeks.

Septicemia

The incidence of hospitalizations for septicemia among renal transplant recipients is approximately 42 times that of the general population. The urinary tract is the most common source of septicemia, followed by the lungs, the surgical wound site, and the abdomen. Most cases occur within the first six months after transplantation. Among patients with bacteremia, poor outcome is associated with Gram-negative species, multidrug-resistant organisms, and *Candida* species, especially when the empiric antimicrobial therapy is inappropriate or delayed. Some studies suggest that bacterial sepsis increases the risk for CMV infection because of high levels of tumor necrosis factor-α (TNF-α) or dysregulated immune response to CMV in the context of serious bacterial infections. For detection of bloodstream infection, two sets of blood cultures should be obtained before initiation of antimicrobial therapy. If intravascular catheter-associated bacteremia is suspected, the device should be removed and the catheter tip should be cultured.

Pneumonia

The incidence of pneumonia in kidney transplantation is the lowest among all solid organ transplants (8 to 16 percent). However, pneumonia is the most serious infection, leading to death in up to 50 percent of cases. The infectious agent in the majority of patients is never determined. This is likely because of the low yield of blood and sputum cultures and the efficacy of antibacterial therapy. In patients who are hypoxic on presentation or do not respond to initial therapy, a bronchoscopy and bronchoalveolar lavage (BAL) is almost always warranted. Patients should be referred if possible to a transplant center to improve the likelihood of diagnosing the etiologic agent. Common causative organisms include *Streptococcus pneumoniae*, nontypable *Haemophilus influenzae*, *Moraxella catarrhalis*, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, and respiratory viruses such as influenza, adenovirus, and respiratory syncytial virus (RSV). Less commonly, patients may present with opportunistic organisms such as *P. jirovecii* and *L. pneumophila*. Silver stains for direct fluorescent antibody for *Pneumocystis* should be done on sputum or BAL specimens. A urine *Legionella* antigen test should be done on all patients on initial work up.

Mycobaterium tuberculosis

Among the infections, tuberculosis is an important cause of morbidity in renal transplant recipients in developing world. The incidence of post-transplant tuberculosis in India has been reported to be highest in the world at 5.7 to 10 percent in various studies. Most cases of *Mycobacterium tuberculosis* infection in kidney transplant recipients are due to reactivation of latent tuberculosis lesions. Important risk factors for reactivation include nonwhite race, history of active tuberculosis, presence of marked abnormality on a chest radiograph, exposure to person with a confirmed case of tuberculosis, and skin test positivity. In transplant patients, the clinical presentation of tuberculosis may be atypical and extrapulmonary and miliary tuberculosis is seen more frequently than in the normal population.

Tuberculosis presents numerous diagnostic difficulties in renal transplant recipients. Because of high frequency of anergy in immunosupressed patients, the Mantoux test is generally unhelpful as a diagnostic tool. The classic picture of apical involvement in the general chest X-ray is seen in only a minority of renal transplant recipients with pulmonary tuberculosis. Demonstration of acid-fast bacilli in the sputum smear requires repeated examination on several occasions and has a low yield. Identification on culture takes four to six weeks.

Treatment of post-transplant tuberculosis presents problems both in the choice of antitubercular agents and in the duration of therapy. Rifampicin is a well-known hepatic P-450 microsomal enzyme inducer, increasing the clearance of both prednisolone and cyclosporine A. The dose of prednisolone needs to be doubled and that of cyclosporine increased to three- to four-fold to maintain therapeutic blood levels. The latter increases the cost of therapy and is unacceptable to a vast majority of patients. An alternative regime that has been successfully used for these patients consists of a combination of isoniazid, pyrazinamide, ofloxacin, and ethambutol. The optimum duration of therapy is also a matter of debate but is usually for 9 to 12 months. The duration needs to be increased to 18 months in patients who are on cyclosporine and are not receiving rifampicin. The role of INH prophylaxis after transplant in endemic areas is controversial.

Cytomegalovirus (CMV)

CMV is a significant cause of morbidity and mortality among kidney transplant recipients. Between 60 and 90 percent of adults are seropositive. Symptomatic disease ranges from a relatively mild syndrome of fever, leukopenia, thrombocytopenia, and elevated liver enzymes to severe disseminated disease that involves multiple organ systems, such as the lung, liver, and GI tract. CMV disease has been implicated as a cause of acute and chronic graft dysfunction as well as long-term graft loss. CMV can also suppress the immune response which predisposes the host to infections with other viruses, bacteria, and fungi.

The incidence and severity of CMV disease has been most strongly associated with the CMV serostatus of the kidney donor and recipient. Seronegative recipients who receive a kidney from a seropositive donor (D+/R-) are at greatest risk for severe primary infection during the first three months post-transplant. Rapid and accurate diagnosis of CMV is important because delayed recognition results in increased morbidity. Quantitative real-time polymerase chain reaction assays for CMV DNA and pp65 antigen detections are the most commonly used means to detect CMV viremia. The shell vial viral culture method remains a reliable way of detecting CMV in sputum.

Multiple strategies have been used to reduce the morbidity and mortality of CMV infection and its associated costs (see Table 4). Avoiding CMV sero-mismatching through organ allocation is not feasible or worthwhile. *Universal prophylaxis* refers to giving prophylactic therapy to all kidney transplant patients regardless of their CMV serostatus. *Selected prophylaxis* refers to giving prophylaxis to patients at high risk for CMV, namely the D+/R- category or those receiving lymphocyte-depleting therapy. The *preemptive treatment* approach treats asymptomatic CMV infection in an effort to prevent CMV disease. Each approach has its advantages and disadvantages, and there is no definitive consensus on optimal preventive strategy.

Prophylactic Therapy

Prophylactic therapy is effective in preventing CMV disease in high-risk patients. Ganciclovir and valganciclovir are equally efficacious. Ganciclovir 1,000 mg PO three times daily and valganciclovir 900 mg PO once daily are used. Valganciclovir is contraindicated in patients with a creatinine clearance of less than 10 ml/h. Prophylactic therapy is usually given during the first 100 days post-kidney transplant. A concern with the prophylactic strategy is that 20 to 30 percent of high-risk patients go on to develop late-onset CMV disease after the prophylaxis is stopped, and the incidence of ganciclovir resistance may be higher in those who receive prophylaxis.

Preemptive Therapy

Preemptive therapy of CMV infection involves monitoring for CMV viremia and starting treatment before the development of signs or symptoms of disease. It has been shown to be as effective as prophylactic therapy in preventing CMV disease. Both oral ganciclovir and valganciclovir have been shown to be effective in treating viremia. Preemptive therapy has the advantage of avoiding the costs and complications of antiviral therapy in low-risk patients while at the same time initiating treatment early to avoid symptomatic disease in high-risk patients. It has also been shown to decrease the development of late CMV disease. Its major limitation is the need to perform frequent determinations of CMV viremia.

Ganciclovir Resistance

Ganciclovir resistance is becoming more common among solid-organ transplant recipients. In one study, 6.2 percent of CMV isolates had UL97 or UL54 mutations. Viral strains with mutations in the UL97 gene, which

Table 4. Antiviral strategies for CMV

Strategy	*Patient*	*Drugs*
Prophylactic	High-risk	Ganciclovir
*Pre-emptive	Replication	Valganciclovir
Therapeutic	Disease	Foscarnet
		Cidofovir
		CMV IVIg

*Detection of replication before disease encodes for a viral protein kinase, remain susceptible to foscarnet and cidofovir. Mutations in the UL54 gene that encodes DNA polymerase can result in resistance to ganciclovir, foscarnet, and cidofovir. The emergence of ganciclovir-resistant CMV underscores the importance of optimizing preventive strategies.

BK Virus (BKV)

BKV is associated with post-transplantation nephropathy, hemorrhagic cystitis, and ureteral obstruction. It has a tropism for genitourinary tract and usually remains dormant in the urinary tract and circulating leukocytes after the primary childhood infection and becomes reactivated during immunosuppression. Adult seroprevalence rates for BKV range from 65 to 90 percent and BKV reactivation can come from the recipient or the donor. BK viremia occurs in 13 percent and BK nephropathy in 8 percent of kidney transplant recipients. Analysis of risk factors for reactivation has underscored the central role played by serologic status of the donor, immunosuppressive regimens, injury to the uroepithelial tissue, and acute rejection. Distinguishing between BK infection and allograft rejection is of paramount importance, since BK infection necessitates reducing immunosuppression and allograft rejection requires the opposite.

Among kidney transplant recipients who are receiving immunosuppressive therapy, 10 to 60 percent have reactivation of BKV accompanied by shedding of urothelial cells. Shedding is inconsistently associated with allograft dysfunction. Once the virus has reactivated, an ascending infection via cell-to-cell spread occurs. The overall state of immunosuppression is the primary determinant of BKV reactivation. Viral replication begins early after transplantation and progresses through detectable stages—viruria, then viremia, then nephropathy. Viruria can be detected by PCR for BKV DNA, reverse transcription (RT)-PCR for BKV RNA, cytology for BKV inclusion bearing epithelial cells termed "decoy cells," or electron microscopy for viral particles. Viremia is a better predictor of nephropathy than viruria. Although higher levels of viremia correlate with the risk of developing nephropathy, there are no established thresholds of viremia to indicate nephropathy.

The gold standard for establishing BK nephropathy remains a kidney biopsy with positive immunohistochemical or immunofluorescent staining for the SV-40 large T antigen. An effective screening strategy is to check blood for BKV DNA by PCR monthly for the first 3 months and at 6 and 12 months after transplantation, at the time of any unexplained rise in serum creatinine, and after augmentation of immunosuppression. Because BKV nephropathy is preceded by BK viremia, asymptomatic BK viremia should prompt empiric immunosuppression reduction and continued monitoring (see Fig. 1).

Currently, no established antiviral treatment is available, and control of viral infection is tentatively obtained by means of reduction of immunosuppression. Treatment attempts have included immunoglobulins without proof of efficacy. Other options include deoxyspergualin, cidofovir, leflunomide, fluoroquinolones and gyrase inhibitors. Cidofovir use is limited by its nephrotoxicity.

Fungal Infections

The incidence of fungal infections in renal transplant recipients is less than that reported for other solid organ transplant recipients, the mortality from fungal infections remains high and is related to the pathogenicity of the

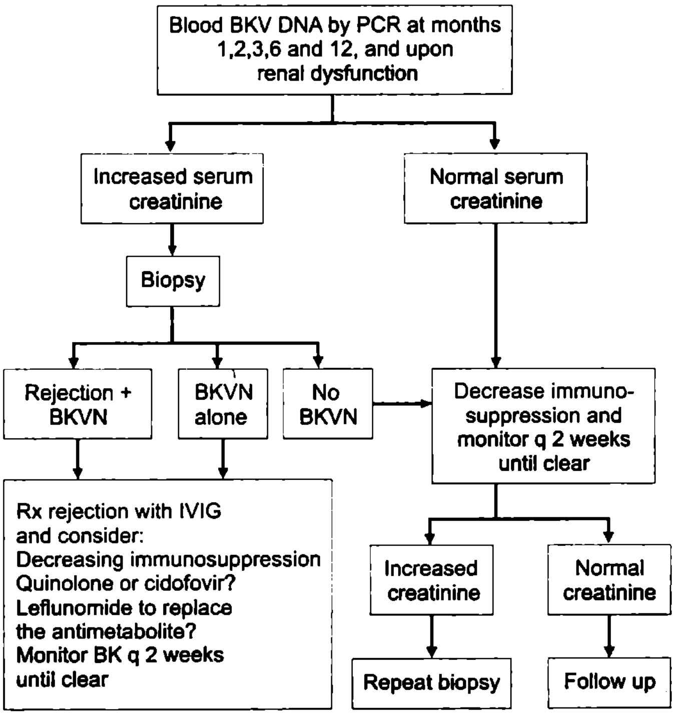
Blood BKV DNA by PCR at months 1,2,3,6 and 12, and upon renal dysfunction
Increased serum creatinine
Normal serum creatinine
Biopsy
Rejection + BKVN
BKVN alone
No BKVN
Decrease immuno-suppression and monitor q 2 weeks until clear
Rx rejection with IVIG and consider:
Decreasing immunosuppression
Quinolone or cidofovir?
Leflunomide to replace the antimetabolite?
Monitor BK q 2 weeks until clear
Increased creatinine
Normal creatinine
Repeat biopsy
Follow up

Figure 1: BK monitoring algorithm

organisms, site of infection, impaired host inflammatory response, limited diagnostic tools, potential for rapid clinical progression, failure to recognize a high-risk patient, and comorbidities, such as renal failure and diabetes mellitus.

Colonization with yeasts and molds occurs frequently in transplant candidates with ESRD and after transplantation because of exposure to broad-spectrum antibacterial agents, domiciliary and hospital exposures, immunosuppressive therapy, especially corticosteroids, and the presence of urinary catheters and endotracheal tubes. Isolation of *Candida* species from cultures of stool, respiratory, and urine samples occurs commonly in kidney transplant recipients receiving corticosteroids and broad-spectrum antimicrobials and does not necessarily imply infection. However, repeatedly positive fungal cultures from a single or from multiple sites may herald invasive candidiasis in the appropriate clinical setting.

Candida species, *Aspergillus* species, *P. jiroveci*, and *C. neoformans* are the most common fungal pathogens reported in renal transplant recipients.

Candida infections occur most commonly during the first month following transplantation and are usually associated with transplant surgical technical complications, early rejection, and enhanced immunosuppression. *Candida* infection is most commonly associated with an endogenous source of colonization. *C. albicans* is the most common species, followed by *C. glabrata*, *C. tropicalis*, and *C. parapsilosis*. Speciation is clinically useful because nonalbicans *Candida* species vary in in vitro susceptibility to amphotericin B and azoles. Sites of *Candida* infection include mucocutaneous candidiasis and esophagitis; wound infections; cystitis, pyelonephritis, and ureteral obstruction by *Candida* elements or "fungal ball"; intra-abdominal infections, including infected perigraft fluid collections or peritonitis; and intravascular device-associated fungemia. Renal parenchymal infection most often results from candidemia and hematogenous spread, although ascending infection from the bladder can occur. Candiduria is typically asymptomatic but may be associated with cystitis or upper tract infection. Patients with genitourinary tract stents and recurrent funguria often require removal of foreign body to eradicate the infection.

Cryptococcus often presents as meningitis but may cause space-occupying brain lesions; pulmonary, dermatologic, skeletal, organ-specific disease; aspergillosis-pneumonia and other tissue-invasive forms, including genitourinary, central nervous system, rhinocerebral, GI, skin, wound, and musculoskeletal disease. Patients at risk for aspergillosis include those receiving repeated courses of enhanced immunosuppression for rejection and those with chronic graft dysfunction, diabetes, comorbid medical illnesses, or CMV infection. Diagnosis of aspergillus infection depends on a high clinical suspicion, isolation of Aspergillus species from a sterile body site or repeated isolation from the respiratory tract, and typical radiographic findings. Radiologic appearances of pulmonary aspergillosis in kidney transplant recipients include nodules, diffuse or wedge-shaped opacities, empyema, or cavitary forms. Serial measurement of aspergillus galactomannan in the serum may aid in the early diagnosis of invasive aspergillosis in the high-risk setting.

Historically, invasive candidiasis, cryptococcosis, coccidioidomycosis, histoplasmosis, and aspergillosis were treated with amphotericin B deoxycholate (AmB). The lipid formulations of amphotericin B are all associated with lower risks for nephrotoxicity, metabolic derangements, and infusion-associated side effects than is AmB. Higher therapeutic dosages can be administered, and broad-spectrum antifungal activity is generally maintained.

Voriconazole appears to be superior to conventional AmB for the treatment of invasive aspergillosis and also has in vitro activity against a wider range of organisms. Available in both intravenous and oral formulations, the drug is generally well-tolerated, but some patients experience visual hallucinations or severe photosensitivity. Oral posaconazole has excellent activity in vitro against *Candida*, *Aspergillus*, and Mucor species, but experience in solid organ transplant recipients is limited to date. Although itraconazole has good in vitro activity against Aspergillus species, its use is generally reserved for treatment of less-severe aspergillosis or maintenance therapy following initial response to lipid amphotericin or voriconazole and for treatment of endemic mycoses. Fluconazole is the first-line agent of the treatment or prevention of reactivation of coccidioidomycosis in renal transplant recipients. The echinocandins, including caspofungin, anidulafungin, and micafungin, inhibit synthesis of fungal cell wall protein $\beta_{1\text{-}3}$ glucan and are fungicidal for *Candida* species, including fluconazole-resistant species. Available only as intravenous formulations, the echinocandins are effective, well tolerated, and have few drug-drug interactions.

HYPERTENSION

The prevalence of post-transplant hypertension in calcineurin inhibitor (CNI) treated renal allograft recipients ranges from 35 percent to 80 percent. Patients are less likely to be hypertensive if their immunosuppressive drug regimen does not include a CNI. The impact of renal denervation following transplantation with loss of renoprotective autoregulation may also play a role in hypertensive transplant injury.

The causes of post-transplantation hypertension are varied and include CNI use, prednisone, preexisting hypertension, primary kidney disease, kidney transplant artery stenosis, and graft dysfunction (see Table 5). Systolic and diastolic hypertension both are independent risk factors for graft and patient loss in kidney transplant recipients.

Both the seventh report of the Joint National Committee and K/DOQI guidelines recommended a target BP of 130/80 mmHg in patients with CKD, although only K/DOQI specifically addresses BP targets in renal transplant recipients.

Lifestyle modifications are necessary and should include weight reduction, a DASH (Dietary Approaches to Stop Hypertension) eating plan, dietary sodium reduction, and physical activity. All classes of antihypertensive drugs have been used in transplant patients, yet no preferred agents are offered by any of the guidelines. Initial efficacy studies suggested that calcium channel blockers might have greater benefit in achieving BP control and limiting graft loss, but it has not been shown that calcium channel blockers have a clear benefit over ACEI on long-term kidney allograft function and survival. Furthermore, these drugs may be involved in the development of edema and CsA-induced gingival hyperplasia.

The use of diuretics in hypertensive renal transplant patients may be effective and often is necessary in combination therapies. These drugs may result in hypercalcemia, hyponatremia, hyperuricemia, and impaired glucose/lipid metabolism in a high-risk group of patients. In summary, a target BP of <130/80 mmHg with lower BP levels (<125/75 mmHg if proteinuria >1 g/d) is recommended in renal transplant recipients. Combination therapy frequently is required to control post-transplantation hypertension; regardless of the agents selected, a close follow up (weekly for two weeks, then monthly) of BP, serum creatinine, electrolytes, and hemoglobin (Hb) levels (in case of ACEI and ARB use) is recommended. It is advised to avoid making changes in BP medications concomitant (within one week) with changes in immunosuppression. This may complicate the differential diagnosis in case of a rapid rise in serum creatinine levels.

METABOLIC COMPLICATIONS

Dyslipidemia

Dyslipidemia, alone or as part of the metabolic syndrome, is an established risk factor for CVD mortality in kidney transplant recipients, as it is in the general population. Post-transplantation hyperlipidemia affects 60 to 80 percent of patients and is associated with immunosuppressive treatment, including sirolimus, corticosteroids, and cyclosporin A. Other factors, such as preexisting familial dyslipidemia, obesity, kidney dysfunction, proteinuria, and diabetes, also contribute to post-transplantation hyperlipidemia.

The evaluation and treatment of post-transplantation dyslipidemia should be based on the National Cholesterol Education Program III and the NKF K/DOQI clinical practice guidelines. Dyslipidemia in kidney transplant recipients should be evaluated at baseline, two to three

Table 5. Different mechanisms that contribute to hypertension after kidney transplantation

Pretransplant Factors	*Post-transplant Factors*
Increased vascular stiffness	Volume overload
Vascular calcification	Delayed allograft function
	Immunosuppression medications
	CNIs
	Corticosteroids
	Transplant renal artery stenosis
	Presence of native kidneys

months after a change in treatment, and at least annually thereafter. Recommended goals are target LDL, nonHDL cholesterol, and triglyceride levels of <100, 130, and 150 mg/dL, respectively. Treatment options include modification of the immunosuppressive regimen when possible, therapeutic lifestyle changes, statins, fibrates, nicotinic acid, and bile acid sequestrants. All statins can provide a 30 to 40 percent reduction in LDL cholesterol levels. For the treatment of hypertriglyceridemia, particularly in patients who are treated with sirolimus, gemfibrozil may be the fibric derivative of choice. Although nicotinic acid derivatives also could be used, fibric acid derivatives are better tolerated. Antilipemic drugs may have significant interactions between the classes and with immunosuppressant agents. Statins and fibrates interact with CNI and may result in hepatitis, myositis, and rhabdomyolysis. In summary, adult renal transplant recipients with hypertriglyceridemia (triglycerides >300 mg/dL, or 5.65 mmol/L) may be treated with fibrates, and statins can be used for LDL cholesterol levels of >100 mg/dL (2.59 mmol/L). Treatment of proteinuria and other causes of secondary dyslipidemia, along with therapeutic lifestyle changes including diet and physical activity, always should be combined. Monitoring of treatment efficacy and observing for clinical and biologic signs of myositis and hepatitis with most current antilipemic agents are recommended.

Diabetes

New-onset diabetes after transplantation (NODAT) is defined using the definition of diabetes and impaired glucose tolerance by the World Health Organization and the American Diabetes Association. Fasting plasma glucose levels ≥126 mg/dL (7 mmol/L) or 2-h plasma glucose levels ≥200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test defines diabetes. NODAT has a high incidence in kidney transplant recipients (up to 25 percent) and significantly decreases patient and graft survival, and its prevalence increases continuously with time. Immunosuppressive therapy with tacrolimus, older recipient age, deceased donor status, hepatitis C, rejection episodes, black race, and higher body weight all are independent risk factors for NODAT (see Table 6).

Therapy for all kidney transplant recipients with diabetes should be directed at achievable targets, including BP <130/80 mmHg, fasting plasma glucose <126 mg/dL, glycosylated Hb ≤6.5 g/dl, urine protein:creatinine ratio ≤200 mg/g, and LDL <100 mg/dL. NODAT has been identified as one of the most important factors associated with reduced graft function and patient and graft survival. Diet control, exercise, and insulin when 2-h plasma glucose levels ≥200 mg/dL (11.1 mmol/L) are essential therapy for diabetes. Oral agents can be used as a supplement but not as a substitute for insulin.

HEMATOLOGIC DISORDERS

Anemia

Anemia is common after renal transplantation. It has been estimated that 25 percent of patients are anemic 12 months after transplantation. Anemia has been associated with worse patient and graft survival and higher rates of acute rejection compared with nonanemic transplant recipients. Unrecognized iron deficiency is a frequent cause, and GI bleeding should be excluded. In the late post-transplantation period, anemia is most commonly caused by immunosuppression or decreased renal function. Azathioprine, mycophenolic acid, and sirolimus can cause anemia, thrombocytopenia, and leukopenia, and the doses of these medications may need to be reduced. Anemia has been reported in as many as 60 percent of patients receiving sirolimus. ACEIs and ARBs may also cause anemia. Parvovirus infection may be a cause of refractory anemia, and treatment with intravenous immune globulin might be effective. When no underlying cause can be found, renal function is impaired, and iron stores are adequate, erythropoietin or darbepoetin alfa may be indicated. Anemia in patients with chronic allograft failure should be treated no less aggressively than the anemia accompanying other causes of chronic renal failure.

Table 6. Risk factors for new-onset diabetes after transplantation (NODAT)

Recipient characteristics	*Donor*
Older age (>45 yrs)	Deceased donor
Higher body mass index (≥30)	Male gender
Family history of diabetes	Tacrolimus use
	HLA mismatch
	Acute rejection
	HCV infection

Erythrocytosis

Erythrocytosis is encountered in up to 20 percent of patients after transplantation, most commonly during the first two years. It rarely occurs in patients who have undergone native kidney nephrectomy although it may be associated with stenosis of the transplant renal artery. Erythrocytosis is not directly related to erythropoietin levels, which may be low or undetectable in some cases. Elevated levels of insulin-like growth factor-1 (IGF-1) have been found, which may increase the sensitivity of erythroid precursors to erythropoietin. Hematocrit levels higher than 60 percent are associated with increased viscosity and thrombosis, and treatment should commence at a hematocrit level of greater than 55 percent. Low doses of ACEIs and ARBs are generally effective in reducing elevated hematocrit levels. Theophylline is a potential alternative to the use of ACEIs or ARBs, although it is less-well tolerated. Phlebotomy may be required in resistant cases.

BONE METABOLISM AND DISEASE

Almost all kidney transplant recipients have some degree of osteodystrophy (disorders of bone remodeling and modeling) that persists after kidney transplantation. The incidence of osteoporosis (bone mineral density ≤2.5 SD below the young adult mean value or T score) approximates 60 percent, and it results in significant morbidity and mortality, including avascular necrosis and fractures. Maximum bone loss occurs within the first three to six months post transplantation and continues during the later stages at a slower rate. Etiologic features include treatment with corticosteroids and CNI, previous osteodystrophy, persistent hyperparathyroidism, hypogonadism, metabolic acidosis, and smoking. Serum calcium, phosphorus, and intact parathyroid hormone levels should be followed regularly and annual assessment of bone mineral density with dual energy X-ray absorptiometry scan of the lumbar spine and the dominant hip should be done at least for the initial three years post-transplant. Treatment strategies to reduce bone loss include testosterone/estrogen replacement when appropriate, elemental calcium and vitamin D, phosphate binders, correction of metabolic acidosis, weight-bearing exercise, and oral or intravenous bisphosphonates. Bisphosphonates increase the risk for adynamic bone disease and should be used cautiously in patients with impaired kidney function after the first year.

β2 Microglobulin (β2M) Amyloidosis

The recovery of normal renal function in renal graft recipients leads to the regression of β2M-associated disturbances of bone metabolism. Articular β2M deposits are frequently present and may remain detectable 10 years after transplantation. β2M amyloidosis may promote local inflammation and thereby favor chronic destructive arthropathy. Therefore, symptomatic patients with localized bone pain and no other diagnosis should be additionally screened for β2M amyloidosis using X-ray, MRI, bone scintigraphy, or a biopsy. Fortunately, in the majority of patients the clinical expression of β 2M amyloidosis decreases or even disappears after renal transplantation.

MALIGNANCIES

Post-transplantation malignancies are a major cause of mortality in kidney transplant recipients. The cumulative prevalence of malignancy increases with the duration of follow up. After 10 years, the risk of cancer in transplant patients was recently reported as being 13.8-fold higher in transplant recipients than in the background population and it is 10 times than those on hemodialysis.

General and more transplant-specific factors contribute to the increased incidence of malignancies in this patient population (see Table 7). These include age, smoking, immunosuppression, and chronic viral infections. The relative risk for cancer depends on the type of malignancy. It ranges from a two- to three-fold increase for common malignancies such as lung, prostate, breast, and colon to up to a 100-fold increase for entities such as Kaposi's sarcomas, post-transplantation lymphoproliferative disease and nonmelanomatous skin cancers.

Carcinomas of the skin and lips are the most common malignancies in renal allograft recipients. Skin cancers in these patients tend to be predominantly of the squamous type, multiple, and more aggressive than in the general population. They are also more likely to affect younger individuals. Patients with a high level of sun exposure and human papilloma virus (HPV) infection are particularly at high risk for skin cancer. HPV also increases the risk

Table 7. Malignancies after renal transplantation—risk factors

Immunosuppression
Conventional risk factors, *i.e.*, age, smoking
Chronic viral infection
Genetic risk factors
History of treatment with cytotoxic agents, *i.e.*,
Cyclophosphamide, chlorambucil

Table 8. Viruses related to malignancies after transplantation

EBV	Lymphoma
HHV 8	Kaposi sarcoma, Lymphoma
Human papillomaviruses (HPV)	Carcinoma cervix, penis carcinoma, vulvar carcinoma
HPV 58	Bowen disease
HPV 8, 19	Nonmelanoma skin cancer
HPV 16, 20	Skin and tonsillar carcinoma
HCV, HBV	Hepatocellular carcinoma

of anogenital and cervical carcinoma. Viruses related to post-transplant malignancies are presented in Table 8.

Lymphoproliferative disorders arise in 1 to 2 percent of the renal transplant population. The incidence is higher when EBV antibody positive donors donate to EBV antibody negative recipients (e.g., children receiving a live donor transplant from their parent) and is increased if the patient receives augmented immunosuppression or develops CMV. PTLD is a complex group of conditions in which B cells (or less frequently T cells) proliferate and can spread widely to produce a range of conditions ranging from a glandular fever-like syndrome to an obvious lymphoma. In most cases, PTLD is a B cell proliferative state induced by the EBV virus (85 percent). The diagnosis is based on immunohistology that relies on the demonstration of EBV coded proteins expressed in B-cells (e.g., Epstein-Barr nuclear antigen - EBNA). Accurate classification is important and has implications for prognosis and management. Early lesions in which there is no evidence of monoclonality and no oncogene expression behave more like an infection than a cancer and may regress completely with immunosuppression dose reduction.

If diagnosis is delayed and frank malignant transformation has occurred, then additional strategies are required. The anti CD20 humanized monoclonal antibody, rituximab and cytotoxic T lymphocytes (CTL) have been very effective. Figure 2 summarizes the approach to the diagnosis and treatment of PTLD. Despite these forms of therapy, some patients do require conventional cytotoxic therapy when the tumor is life-threatening. There is an increased risk of overwhelming infection when cytotoxic therapy follows on from post-transplant immunosuppression. The antiproliferative characteristics of sirolimus have a salutary impact on the treatment of these malignancies.

After the first post-transplant year, kidney transplant recipients should undergo annual or biannual skin examination. Age-appropriate annual prostate-specific antigen measurements, fecal occult blood testing, digital and rectal examinations, breast examination and mammography, and colonoscopy are indicated as in the nontransplant patient. Unique screening may include hepatobiliary ultrasound and serum α-fetoprotein measurements (history of HBV or HCV) as well as cystoscopy (history of cyclophosphamide use).

KEY POINTS

1. Renal transplantation is the best amongst renal replacement therapies for patients with ESRD.
2. Based on the net state of immunosuppression and resultant risk for infectious complication along with the surgical complications seen early after transplantation, the post-transplant period is divided into an early (<three months) and late period.
3. One should be vigilant in the immediate post-transplant period for the surgical complications as their initial presentation is no different from medical causes.
4. Prompt diagnosis of the cause of allograft dysfunction and early detection of infectious complications along with institution of appropriate therapies is important to improve the outcomes of renal allograft recipients.
5. A delicate balance should be maintained between the amount of immunosuppression to prevent allograft rejection and the side effects that are related to medications as well as immunosuppression.

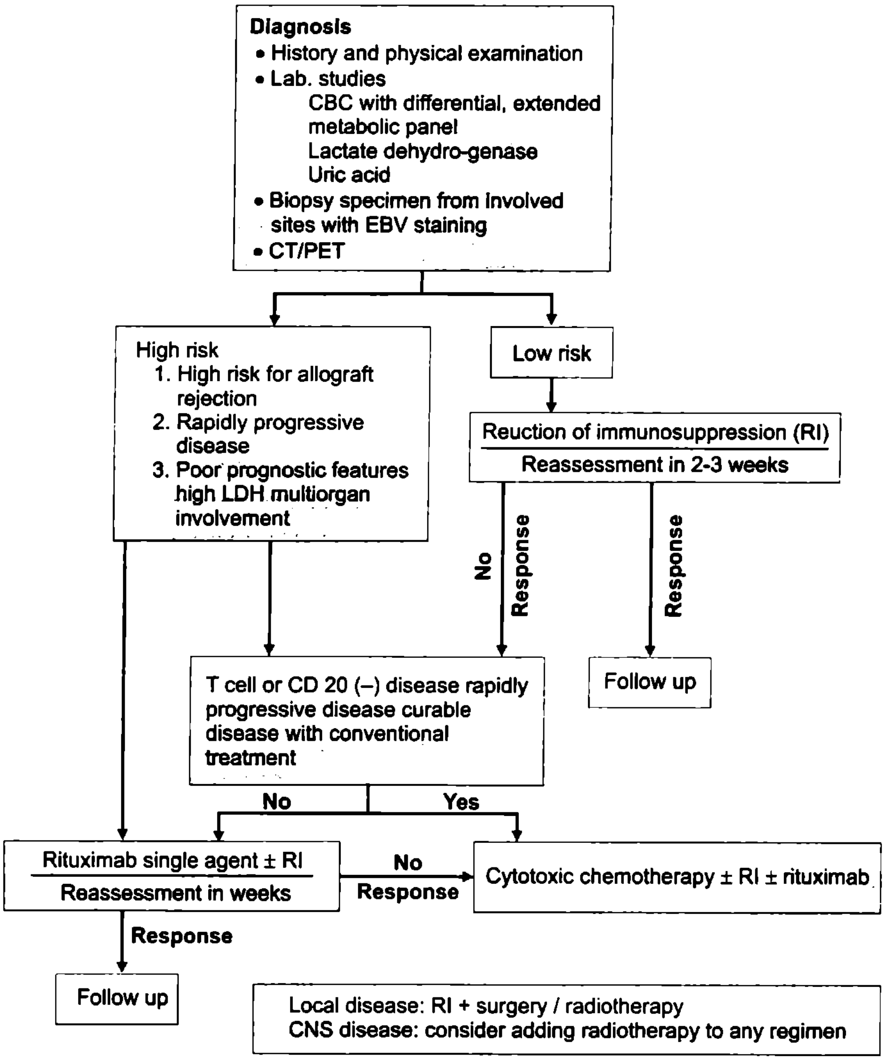
Diagnosis
• History and physical examination
• Lab. studies
CBC with differential, extended metabolic panel
Lactate dehydro-genase
Uric acid
• Biopsy specimen from involved sites with EBV staining
• CT/PET
High risk
1. High risk for allograft rejection
2. Rapidly progressive disease
3. Poor prognostic features high LDH multiorgan involvement
Low risk
Reuction of immunosuppression (RI)
Reassessment in 2-3 weeks
No Response
Response
T cell or CD 20 (–) disease rapidly progressive disease curable disease with conventional treatment
Follow up
No
Yes
Rituximab single agent ± RI
Reassessment in weeks
No Response
Cytotoxic chemotherapy ± RI ± rituximab
Response
Follow up
Local disease: RI + surgery / radiotherapy
CNS disease: consider adding radiotherapy to any regimen

Figure 2: Diagnosis and treatment of post-transplant lymphoproliferative disorder (PTLD)

6. Measures for prevention of cardiovascular and metabolic complications may further reduce the post-transplant morbidity and mortality.

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LIST OF ABBREVIATIONS

- ACE-I: angiotensin-converting enzyme inhibitor
- AmB: amphotericin B deoxycholate
- ARB: angiotensin receptor blocker
- BAL: bronchoalveolar lavage
- BKV: BK virus
- β2M: β2 Microglobulin
- CKD: chronic kidney disease
- CMV: cytomegalovirus
- CNI: calcineurin inhibitors
- CT: computed tomography
- CVD: cardiovascular disease
- DASH: dietary approaches to stop hypertension
- DFA: direct fluorescent antibody
- DNA: deoxyribonucleic acid
- DVT: deep venous thrombosis
- EBV: epstein-barr virus
- ESRD: end-stage renal disease
- GI: gastrointestinal
- HBV: hepatitis B virus
- HCV: hepatitis C virus
- HDL: high-density lipoprotein
- HIV: human immunodeficiency virus
- HLA: human leukocyte antigen
- HPV: Human papillomaviruses
- HSV: herpes simplex virus
- IGF-1: insulin-like growth factor-1
- KDOQI: kidney disease outcomes quality initiative
- LCMV: lymphocytic choriomeningitis virus
- LDL: low-density lipoprotein
- MRI: magnetic resonance imaging
- MRSA: methicillin-resistant *Staphylococcus aureus*
- NKF: *National Kidney Foundation*
- NODAT: new-onset diabetes after transplantation
- PCP: *Pneumocystis carinii* pneumonia
- PCR: polymerase chain reaction
- PML: progressive multifocal leukoencephalopathy
- PTLD: post-transplantation lymphoproliferative disorder
- RNA: ribonucleic acid
- RSV: respiratory syncytial virus
- SARS: severe acute respiratory syndrome
- TNF: tumor necrosis factor α
- TRAS: transplant renal artery stenosis
- UTI: urinary tract infection
- VRE: vancomycin-resistant *Enterococcus faecalis*
- VZV: varicella-zoster virus

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Postrenal Transplantation Late Complications Including Rejection

Todd E Pesavento

The first successful kidney transplant was performed in 1954 between two identical twins by Dr Joseph Murray. This miraculous feat was slowly duplicated and over the next decade remarkable advancements occurred that allowed transplantation to be offered to a broader range of patients, with organs emanating not just from closely related living donors but also from distantly related live donors to deceased donors. By 1965, amazing short-term graft survival had been achieved, reaching nearly 80 percent from living donor sources and approaching 65 percent for deceased donor recipients.

We now take renal transplantation as an accepted, standard therapy for end-stage renal disease (ESRD). What was once a rare, life-saving procedure with an uncertain outcome has evolved into a therapy that is just as life-saving but now performed on a daily basis with greatly improved success for both the short and long term. Limitations to successful renal transplantation are now not due to lack of effective medications, but rather a severe organ shortage. Since the last edition of this book, tremendous advancements in renal transplantation have been made that have allowed the successful transplantation of many patients that were previously excluded from transplantation-highly sensitized patients, the elderly, those with human immunodeficiency virus (HIV) as well as the more routine use of extended criteria donor kidneys. Even with the heightened acuity of illness of recipients today, acute rejection is now routinely less than 10 percent, one—year patient and graft survival approach or exceed 90 percent and the half-life of living donor transplantation exceeds two decades. These factors, along with the ever-increasing volume of patients with kidney disease, make it paramount that all nephrologists understand and are equipped to handle the complexity of today's renal transplant patients.

IMMUNOSUPPRESSIVE AGENTS

A detailed discussion of immunosuppressive medications is beyond the scope of this text but a working knowledge of the currently used agents is important for all nephrologists caring for renal transplant recipients. While there was a proliferation of new immunosuppressive agents in the last decade, there have been relatively fewer novel immunosuppressive agents introduced in the market recently. Prior to 1984, most transplant recipients were treated only with azathioprine and corticosteroids. With the advent of cyclosporine, double therapy (cyclosporine and prednisone) or triple therapy (cyclosporine, prednisone and azathioprine) quickly became standard therapy. In the last few years there has been the addition of mycophenolate, tacrolimus, rapamycin (sirolimus), everolimus, and induction agents including interleukin-2 receptor antagonists, anti-thymocyte globulin and alemtuzumab. More recently, the transplant community has evolved to using different agents for unique patient populations. As such, there is currently no one "standard" therapy between centers or even within a single center, although the combination of tacrolimus and mycophenolate (+/- glucocorticoids) is a widely used combination. Patients may receive certain agents now based on their risk for rejection, quality of organ they received, alloantibody status and overall side effect profile of each individual agent.

Glucocorticoids

These agents remain standard therapy for almost all patients very early post-transplant. In part because of their anti-rejection properties as well as to minimize cytokine release syndrome from induction agents, high dose IV steroids (250 to 1000 mg daily for three to five days) is commonly used. With more potent induction agents, as well as better maintenance immunosuppressive agents, rapid steroid weaning and elimination in the first week post-transplant has quickly been adopted by many transplant center with results equal to or better than long-term therapy with glucocorticoids, even in high risk patients. For centers that continue with long-term therapy, a maintenance dose ultimately of 0.1 to 0.15 mg/kg is generally recommended. Due to the well-known long-term complications of steroids (hypertension, obesity, diabetes, vascular, skeletal and skin complications) in those patients already receiving maintenance therapy, there has always been a desire for steroid-free immunosuppression. This may be possible in well selected, stable recipients, but even in the era of the newer, more potent immunosuppressive agents, acute rejection still occurs between 10 to 30 percent after steroid withdrawal. Although it remains controversial when is the best time to remove glucocorticoid therapy, many recommend early withdrawal in the first weeks of transplantation rather than after prolonged therapy.

Azathioprine

Long a mainstay in immunosuppressive regimens, azathioprine plays a much reduced role in maintenance immunotherapy since the introduction of newer agents. Azathioprine tends to be well-tolerated but reversible leukopenia is seen acutely and long-term use is associated with an increased incidence of cutaneous warts, bone marrow suppression, and skin malignancy. Allopurinol decreases the metabolism of azathioprine and when used concomitantly, the azathioprine dose should be reduced by half.

Cyclosporine

In use for nearly 30 years, cyclosporine, once a mainstay for immunosuppression in renal transplantation, now shares this role with tacrolimus in the category of agents commonly referred to as calcineurin inhibitors (CNI). An improved microemulsion formulation of cyclosporine has been released, Neoral^{R} (Novartis) that has improved pharmacokinetics and allows for improved absorption and reduced intra and interpatient variability. In conjunction with mycophenolate mofetil and glucocorticoids, one-year graft survival rate approaching or exceeding 90 percent is routinely being achieved. Cyclosporine acts by binding to the intracellular protein cyclophilin, resulting in decreased production of interleukin-2. Depending on the method used to measure the drug and the overall function of the allograft, desired cyclosporine trough levels within the first year of 200 to 400 ng/ml and long-term maintenance levels of 100 to 300 ng/ml are reasonable, although this can vary considerably. Two-hour cyclosporine levels (C2 levels) correlate better than trough levels for area under the curve (AUC) for cyclosporine exposure and are recommended for monitoring. C2 levels early post-transplant are recommended to be 800 to 1200 ng/ml with levels of 600 to 800 long term. Intravenous cyclosporine is rarely required with the microemulsion formulation, however, one third of the corresponding oral dose is administered as a continuous infusion to avoid nephrotoxicity in those patients unable to tolerate oral medications.

Although a useful immunosuppressant, cyclosporine has long been considered a two-edged sword requiring a balance between acute rejection prophylaxis and nephrotoxicity along with other side effects including hypertension, hyperlipidemia and neurotoxicity. Cyclosporine is nephrotoxic both acutely and chronically. Acute renal failure is generally hemodynamic, readily reversible and due to vasoconstriction of the afferent arteriole. Diuretics should be used cautiously and nonsteroidal anti-inflammatory agents are best avoided to prevent secondary cyclosporine nephrotoxicity even in stable transplant patients. Chronic cyclosporine nephrotoxicity is more controversial but it is generally agreed upon that cyclosporine causes upregulation of transforming growth factor beta, promotes interstitial fibrosis and chronic arteriolopathy. Nankivell demonstrated by biopsy that histologic lesions consistent with cyclosporine toxicity were seen nearly universally in renal transplant patients by 10 years post-transplantation. While clinically this effect is not manifested in all renal transplant patients, it appears to be more severe in recipients of extra-renal transplants, such as heart, lung or liver, as opposed to the denervated renal allograft. Hypertension is common in cyclosporine treated patients, is complex in origin and is due to a combination of afferent arteriolar vasoconstriction, sodium avidity and endothelin and NO imbalances. Additional side effects include a resting tremor, seizures (especially with hypomagnesemia), gingival hyperplasia and hirsutism; cyclosporine also contributes to the development of post-transplant diabetes and hyperlipidemia.

As cyclosporine remains an important immunosuppressant, it is prudent to emphasize several common drug interactions. Cyclosporine is hepatically metabolized through the cytochrome P-450 3A system. As such, other drugs that are metabolized via this pathway would be expected to alter cyclosporine metabolism. Table 1 lists drugs that commonly interact with cyclosporine. While it is not essential to avoid these medications, most transplant physicians prefer to utilize other medications if possible to avoid either precipitating toxicity (due to enhanced cyclosporine levels) or acute rejection (due to reduced cyclosporine levels). Although not as well studied, medications affecting cyclosporine metabolism typically have the same effect on tacrolimus and rapamycin.

Tacrolimus (FK-506)

Tacrolimus is derived from the fungus *Streptomyces tsukubaensis* and is a macrolide antibiotic. It is a CNI and binds to the intracellular protein, FK binding protein, ultimately resulting in decreased production of interleukin-2. While it is chemically and structurally distinct from cyclosporine it shares many of the immunosuppressive properties and side effect profile. Initially used in liver transplant recipients, it has become a mainstay for all solid organ transplants. Tacrolimus is often used at a dose of 0.1 mg/kg twice daily aiming for trough levels of 10 to 15 ng/ml early post-transplant and 5 to 10 ng/ml in long-term patients. Intravenous tacrolimus is highly toxic and is not recommended; in hospitalized patients, it can be administered through a nasogastric tube since it is generally well absorbed.

Table 1. Medications interfering with cyclosporine metabolism

Increase CsA levels	*Decrease CsA levels*
Danazol	Carbamazepine
Diltiazem	Phenobarbital
Erythromycin	Phenytoin
Fluconazole	Rifampin
Ketoconazole	
Metoclopramide	
Nicardipine	
Verapamil	

Side effects of tacrolimus tend to mirror those of cyclosporine. Common, shared side effects of tacrolimus and cyclosporine include nephrotoxicity, hyperkalemia and hypertension. Important differences include neurological complications which are more common with tacrolimus than cyclosporine. Patients are more likely to exhibit tremors, headache and insomnia but can also suffer seizures, psychosis or overt encephalopathy, especially with elevated tacrolimus levels. These side effects appear to be dose related. With more experience lower doses are now being employed and these side effects can be minimized. Glucose intolerance and overt diabetes mellitus can occur with tacrolimus and appears to be more common than in cyclosporine treated patients. Hispanics and blacks appear to be at especially high risk for development of diabetes. Employing lower dosages of glucocorticoids as well as tacrolimus appears to minimize the severity of diabetes. Hyperlipidemia occurs in tacrolimus treated patients but may be less common than in cyclosporine based regimens. While this outcome may be due to lower dosages of glucocorticoids employed, successful treatment of hyperlipidemia has been demonstrated after conversion from cyclosporine to tacrolimus. Gingival hyperplasia and hirsutism occurs less frequently with tacrolimus than with cyclosporine. Conversion to tacrolimus in patients may result in significant resolution of these complications.

Mycophenolate Mofetil

Since being released for clinical use in 1995, mycophenolate mofetil has quickly been adopted as standard therapy for acute rejection prophylaxis in renal transplantation, quickly replacing its well established counterpart, azathioprine. Although mycophenolate, sometimes referred to as simply MMF, is used in place of azathioprine, it has a unique mode of action, is clearly more potent and has been instrumental in CNI sparing regimens and when attempting glucocorticoid withdrawal.

Mycophenolate acts by reversibly inhibiting the enzyme inosine monophosphate dehydrogenase (IMPDH). This enzyme is critical for the *de novo* synthesis of purines. This selective pathway is vital for actively replicating lymphocytes whereas other cell lines can utilize a salvage pathway for production of purines. Unlike other agents, mycophenolate inhibits both T cells as well as B lymphocytes. This feature makes it an intriguing agent for the possible treatment or minimizing damage caused by chronic antibody mediated rejection. In addition to mycophenolate mofetil, a newer enterically coated compound, mycophenolate sodium, is available that may have a more favorable gastrointestinal profile.

Mycophenolate has been well-studied in three large prospective, randomized controlled trials. All three trials demonstrated that MMF reduced the incidence of first acute rejection by nearly 50 percent. Although not statistically powered to show a difference in graft survival, when composite data from all trials have been subsequently analyzed, patients treated with MMF had a superior graft outcome compared to those treated with either placebo or azathioprine. Analysis of the United States Renal Transplant Registry also revealed that MMF reduced late renal allograft loss independent of acute rejection. In an attempt to minimize glucocorticoid and CNI toxicity, studies have suggested that mycophenolate may allow withdrawal of these agents. Even with this potent agent, it is remains difficult to withdraw steroids after long-term use successfully due to a risk of acute rejection; however, further studies have shown the excess risk is seen in predominantly black patients and so this approach may be achievable in other populations. More success has been seen when CNIs are either reduced or eliminated in patients with chronic allograft nephropathy (CAN) under the cover of potent MMF therapy. With this approach, graft function appears to stabilize with a less rapid decline of renal function compared to those patients who remain on full dose CNI therapy.

Mycophenolate is generally well tolerated with the major side effect being gastrointestinal disturbances, generally diarrhea or nausea, although frank bleeding and ulcers can also occur. The GI conditions may improve over time and often respond to dose reduction. Additionally, dose responsive bone marrow suppression, usually leukopenia, may occur. Despite being more potent than azathioprine, an excess of invasive opportunistic infections has not been seen.

Rapamycin (Sirolimus/Everolimus)

A macrolide derivative of *Streptomyces*, rapamycin belongs to a novel immunosuppressive class directed against the mammalian target of rapamycin (mTOR). The two commercially available agents, sirolimus and everolimus, frequently referred to as mTOR inhibitors, inhibit mTOR, a regulatory protein kinase involved in lymphocyte proliferation. These drugs bind to the same intracellular immunophilin as does tacrolimus, i.e., FK binding protein 12. While the tacrolimus-FKBP complex inhibit calcineurin phosphatase and ultimately result in suppressed interleukin-2 transcription, the rapamycin-FKBP bind to mTOR, arrest the progression of G1 to S phase of the cell cycle and therefore inhibit DNA synthesis and cellular proliferation. When used in combination, mTOR inhibitors and CNIs are synergistic and are an incredibly potent with pronounced immunosuppressive effects. This synergistic result has allowed for substantial reductions of both CNI and mTOR dosages and blood levels necessary to achieve rejection prophylaxis.

Sirolimus and everolimus, while structurally similar, do have important pharmacokinetic differences. Sirolimus has a long half-life of 40 to 80 hours, may take 7 to 18 days to reach steady state and is typically dosed once daily. Due to this prolonged time to achieve therapeutic levels, a loading dose is frequently recommended for the first few days. In distinction, everolimus has a much shorter half-life of 18 to 35 hours, has a much reduced time to achieve steady state and is dosed twice daily. Despite structural and pharmacokinetic differences, the side effect profile is similar for both sirolimus and everolimus. Understanding these side effects is essential in allowing for the successful utilization of mTOR inhibitors. The most clinically important feature is the intense inhibition of wound healing. Sirolimus impairs the expression of vascular endothelial growth factor (VEGF), nitric oxide (NO) and diminishes the production of collagen by fibroblasts. These factors result in significantly higher wound complications of 20 to 50 percent post-transplantation compared to other agents. Delayed wound healing, wound dehiscence, lymphocele formation and incisional hernias complicate the usage of mTOR inhibitors and may require restricting usage in certain patient populations, including the elderly, obese, diabetics and those patients receiving corticosteroids. Meticulous surgical technique, nonabsorbable and delayed suture removal are often recommended to avoid complications. Early use of sirolimus has been associated with significantly higher rates of delayed graft function (DGF) as well as delayed renal recovery in those patients with DGF. Other side effects can include mild leucopenia and thrombocytopenia and oral aphthous ulcers that often respond to dose reductions. Hyperlipidemia is common, is often dose dependent and often controlled with statin agents. Hypertriglyceridemia, however, may be difficult to manage and in some cases requires discontinuation of usage.

Sirolimus has been widely studied as part of a strategy to modify CAN and reduce long-term CNI toxicity. A meta-analysis by Mulay, et al., of over 1000 patients demonstrated that CNI withdrawal from a sirolimus based regimen resulted in an improvement of creatinine clearance of nearly 7.5 ml/min at one year compared to continued CNI and sirolimus therapy. There was an incremental difference of acute rejection of 6 percent in the CNI withdrawal patients but no difference in graft loss or patient death. CNI withdrawal also resulted in an improvement of 7 mmHg of systolic blood pressure. Other randomized trials have demonstrated that conversion from a CNI based therapy to sirolimus have detrimental outcomes, especially in those patients with significant renal function or proteinuria at the time of conversion. As a result, it is recommended that conversion from a CNI to sirolimus occurs early (around three months post-transplant) before fixed allograft dysfunction occurs, in the absence of proteinuria and with relatively well-preserved renal function (GFR >30 to 40 ml/min).

An intriguing property of mTOR inhibitors is the anti-tumor properties they possess. Angiogenesis inhibition, anti-proliferation and reduction of VGEF and transforming growth factors have been demonstrated experimentally and clinically with mTOR inhibitors. Recently, various mTOR inhibitors have been approved as treatments for renal cell carcinoma. Numerous randomized transplant trials have shown a significant reduction in malignancy rates in sirolimus treated patients. Several studies have reported a regression of Kaposi's sarcoma and improvement of post-transplant lymphoproliferative disorders when patients were converted from cyclosporine to sirolimus. While there has not been a prospective randomized trial specifically evaluating malignancy reduction in mTOR inhibitor treated patients versus other immunosuppressive agents, the consensus of most experts supports the conversion to this class of drugs in patients with skin cancers and selectively in other solid organ tumors.

Belatacept

This novel compound is a fusion protein that acts to selectively inhibit the costimulatory receptor on T cells (CD28) thereby preventing signal 2 required for T cell activation. At this time, phase III studies have demonstrated that belatacept resulted in superior renal function at 12 months compared to controls treated with CNI despite more frequent and severe acute rejections in the belatacept groups. There is a worrisome finding of excessive intracranial post-transplant lymphoproliferative tumors in patients treated with belatacept but this appears to be more common in EBV negative recipients. This new agent will likely to have an important role in the future to allow CNI reduction early post-transplant but the long-term outcomes are yet to be determined.

ACUTE REJECTION

Acute rejection, until recently, has been common (occurring in nearly 50 percent of renal transplant recipients in the first year post-transplant prior to the adoption of mycophenolate) and was a major cause of graft loss. However, rates of acute rejection are now routinely reported at less than 10 percent. Factors responsible for this dramatic reduction in immunologic events include refinement of immunosuppressive protocols, the introduction of new immunosuppressive agents including tacrolimus, cyclosporine microemulsion, induction therapy with interleukin-2 receptor antagonists and lymphocyte depleting agents, mycophenolate mofetil and sirolimus. With this immunosuppressive armamentarium, graft loss from acute rejection is rare and currently the most common cause of graft failure death with a functioning graft.

Although many techniques are reported to diagnose acute rejection including clinical presentation, nuclear renal scans, measurement of resistance indices on renal ultrasound and determination of various urinary cytokine levels, gene expression profiling or measurement of T cell adensosine triphosphate levels (ATP), none are sensitive or specific enough for routine clinical use. The gold standard for determination of acute rejection is a core needle renal allograft biopsy in the presence of graft dysfunction. Routine assessment for antibody mediated rejection with C4d staining and/or donor specific antibody testing in the presence of graft dysfunction is now standard. Some groups have advocated routine "protocol" biopsies following a successful kidney transplant in hopes of detecting a subclinical "silent" acute rejection. However, this remains controversial and is not routinely performed in the absence of graft dysfunction.

To standardize the interpretation and reporting of renal allograft biopsies, an international consensus panel has proposed the "Banff 97 working classification of renal allograft pathology," *Kidney Int*, 1999. This was subsequently updated in 2009 (*American Journal of Transplantation,* 2010) to reflect the role of antibody mediated acute rejection. This grading schema, summarized in Table 2, creates objective criteria to diagnose and grade acute rejection. Major features of this schema include the distinction between acute cellular tubulointerstitial versus vascular rejection as well as humoral rejection. It is now well established that vasculitus and antibody mediated rejection in a renal allograft biopsy portends a worse prognosis.

Once the diagnosis of acute rejection is made, causative factors need to be determined and corrected. Acute rejection is rare in nonsensitized compliant patients able to tolerate full dosages of immunosuppression. However, patients with acute rejection often have been received reduced immunosuppression due to viral or bacterial infections or other post-transplant complications. Treatment for acute rejection is highly center and patient specific. However, for patients with cellular tubulointerstitial rejection, treatment with high dose glucocorticoids is generally employed first at doses generally 500 to 1000 mg/d for three to five days, so called "pulse therapy". Steroid resistant and acute vascular rejection often receive treatment with an anti-lymphocyte preparation, either monoclonal (such as OKT3) or polyclonal (such as anti-thymocyte globulin), for 10 to 14 days. Humoral acute rejection requires intensive therapy with plasmapheresis and/or intravenous immune globulin (IVIG).

CHRONIC ALLOGRAFT DYSFUNCTION

Previously referred to as chronic rejection, this complex entity had until recently received little attention given the importance of acute rejection as well as the lack of understanding and lack of specific therapy for chronic allograft dysfunction. However, in recent years, tremendous advancements in immunosuppressive regimens have resulted in plummeting rates of acute rejection. The diminution of acute rejection resulted in a new focus on other causes of long-term graft function, namely chronic graft injury. While there is now a greater

Table 2. Summary of Banff 2007 working classification for renal allograft pathology in acute rejection

Type (Grade)	*Histopathologic Finding*
Antibody mediated rejection (acute)	Requires C4d+, circulating anti-donor antibodies and tissue injury (ATN-like inflammation, capillary/glomerular inflammation or thrombosis, or arteritis)
Antibody mediated rejection (chronic)	Requires C4d+, circulating anti-donor antibodies and chronic tissue injury (glomerular double contour, capillary BM multilayering, interstitial fibrosis/tubular atrophy)
Borderline (suspicious for acute rejection)	No arteritis but foci of mild tubulitis (1–4 mononuclear cells/ tubular cross-sectional area)
IA	Interstitial infiltrate with moderate tubulitis (5-10 mononuclear cells/tubular cross-sectional area)
IB	Interstitial infiltrate with severe tubulitis (>10 mononuclear cells/ tubular cross sectional area)
IIA	Mild to moderate intimal arteritis
IIB	Severe intimal arteritis
III	Transmural arteritis and/or fibrinoid changes with necrosis of medial smooth muscle cells

Sis, et al. Banff '09 Meeting Report: Antibody Mediated Graft Deterioration and Implementation of Banff Working Groups. *Amer J Transpl* 2010;10:464-71.

understanding of this process, the continuing changing of the name from chronic rejection to CAN to the currently preferred name of the histologic features of tubular atrophy and interstitial fibrosis, reveals how much additional research is necessary to fully comprehend this condition. Chronic allograft nephropathy, no matter what the cause, is now viewed as one of the most important impediments to long-term success in renal transplantation.

CAN may be defined as the insidious loss of renal function, as evidenced by a rising serum creatinine, more than three months post-transplant, in the absence of other factors when confirmed by a renal biopsy. Despite this definition, there is no specific marker for chronic rejection and even a renal biopsy may be unreliable due to sampling error. Several features are characteristic and include late onset hypertension, low to medium grade proteinuria and a biopsy with interstitial fibrosis, tubular atrophy, transplant glomerulopathy and arterioles with fibrointimal hyperplasia. However, these histologic features may also be caused by cyclosporine and tacrolimus or have been present in the donor (especially in older, hypertensive donors) prior to the transplant.

CAN is likely caused by both immunologic and nonimmunologic injury. The most widely accepted cause of CAN is a prior episode of acute rejection. Acute rejection may induce a cascade of self-propagating events of renal injury followed by inflammation, further immune responses and ultimately more renal injury. Nonimmune events are more numerous and include injury from post-transplant DGF, hypertension, diabetes, hyperlipidemia and decreased nephron mass. CNI toxicity has gained renewed attention as an important, avoidable cause of CAN. CNI-sparing immunosuppressive regimens are now widely being adopted as an attempt to minimize chronic allograft injury.

Once CAN is recognized, aggressive attention to all possible risk factors is mandatory. While there is still no specific therapy for this disorder, there is no role for increased immunosuppression unless the patient experiences a documented acute rejection episode or is noncompliant. De novo development of alloantibodies is increasingly recognized as important factor in transplant glomerulopathy and CAN but successful, long-term therapy is still elusive. The cornerstone of management is aggressive management of hypertension with a systolic blood pressure goal of 120 to 130. Appropriate management of hyperlipidemia, proteinuria and minimizing CNI toxicity are also clearly essential. Taken together, these measures may ultimately prevent premature graft loss.

TRANSPLANTATION OF INCOMPATIBLE RECIPIENTS

One of the tremendous accomplishments of the last decade has been the successful kidney transplantation of recipients who have preformed HLA antigens against their donor or are ABO incompatible. While transplantation against a positive crossmatch is commonly performed in other solid organs, namely heart and liver, high rates of immediate graft loss are common when this is performed in renal transplantation and until recently had been considered a contraindication to transplantation.

Many patients are highly sensitized either through blood transfusions, pregnancy or prior transplantation or do not have an ABO compatible donor. For these patients, their waiting time is significantly longer to receive a transplant and their outcomes are significantly worse than a nonsensitized recipient. In an attempt to ameliorate this situation, several transplant centers have developed strategies to circumvent this obstacle. While it is beyond the scope of this chapter to fully explore this topic, a brief description of the approach to these challenging patients is helpful and the recent review by Gloor and Stegall in Nature Reviews can provide more details.

The cornerstone of management of the highly sensitized patient is reduction of both preformed HLA antibodies and prevention of the anamnestic response of memory B cells following transplantation. Two distinct approaches have yielded similar results—either high dose IVIG or plasmapheresis pre-and post-transplantation followed by low dose IVIG therapy. Regardless of the initial approach used, acute humoral rejection remains common occurring in 30 to 40 percent of patients. Following acute rejection, therapy typically consists of plasmapheresis to lower antibody levels and additional IVIG. Additional therapy to inhibit further antibody mediated damage can include anti-CD20 (rituximab), complement blockade (eculizumab), or more recently proteasome inhibition with bortezomib. Regardless of the therapy used, long-term results are still suboptimal. The resource intensive approach to transplanting this challenging group of patients has raised questions whether the medium and long-term results justify this therapy and as such patients should only be transplanted at experienced centers.

HYPERTENSION

Hypertension is one of the most common of all the complications affecting recipients of solid organ transplantation. The overall prevalence varies according to the type of organ transplanted and the age of the recipient. Over 55 percent of adult recipients of a kidney transplant suffer from hypertension. This increases to 65 to 75 percent of pediatric renal transplant recipients and further, over 80 percent of patients who receive a heart transplant develop hypertension. Because hypertension is so common after transplantation, the etiology so complex and multifactorial, and the fact it can occur in patients who were previously normotensive pretransplant, it is frequently termed post-transplant hypertension. In fact, nearly ninety percent of renal transplant recipients will require at least one antihypertensive agent during the first year post-transplant. The management of post-transplant hypertension continues to receive attention due to the strong correlation of hypertension with allograft failure and cardiovascular death. While post-transplant hypertension has not traditionally received a high priority for management since it was felt that graft dysfunction resulted in hypertension, increasingly studies are suggesting that the reverse may be true and that even mildly unregulated hypertension may cause long lasting graft deterioration. Despite the complex and multifactorial nature of post-transplant hypertension, the pathogenesis of this disease has been well studied and many of the inciting factors have been elucidated. In distinction, "essential hypertension" which affects 90 percent of hypertensive patients in the general population is still widely viewed as idiopathic in etiology.

It is useful to group the causes of post-transplant hypertension into those caused by:

1. medication effect
2. function of the allograft
3. vasculature of the recipient.

Corticosteroids are still commonly used in transplantation and cause sodium retention and may provide excess substrate for angiotensin. The hypertensive effect of corticosteroids generally is dose related and low dose, long term maintenance therapy is generally not a major cause of hypertension. In fact, even after steroid withdrawal, hypertension improves only slightly and may be related to improvement in body weight in addition to its sodium retaining effects. In contrast, cyclosporine and tacrolimus can cause hypertension in the short and long term and appears dose related. Cyclosporine promotes a sodium avid state but has paradoxically been shown to be a low renin condition. This sodium retaining property may be related to the induction of afferent arteriolar vasoconstriction as well as stimulation of the sympathetic nervous activity. CNI induced hypertension may also result from alterations of the endothelin/NO system. There is little evidence that mycophenolate mofetil, azathioprine or sirolimus contribute to post-transplant hypertension.

Impaired renal allograft function and CAN are the most important causes of post-transplant hypertension. Impaired renal function can lead to excessive renin production with activation of the angiotensin system. Additionally, impaired excretory function leads to further sodium retention, volume expansion and elevated renal vascular resistance. The native kidneys can also contribute to hypertension and in cases of severe hypertension refractory to medications and without other causes, bilateral native nephrectomy has been useful.

Vascular causes of hypertension generally reflect chronic damage to small and medium sized intrarenal vessels. While there may be no specific therapy for this situation, aggressive blood pressure control with a target systolic BP less than 130 mmHg, may allow for endothelial healing and ultimate stabilization of the graft. Large vessel renal artery stenosis may account for 5 to 10 percent of post-transplant hypertension. Most patients present 6 to 12 months after transplantation, have severe, refractory hypertension and is more common in recipients of living donor transplants. However, some patients may present simply profoundly volume overloaded or with refractory, massive peripheral edema. Diagnosis is generally made by angiography and the use of digital subtraction angiography (DSA) allows for minimal use of intravenous contrast making this technique relatively safe even in the presence of significant renal dysfunction. Recently, advances in Doppler ultrasound make this a useful modality for diagnosis, however, it remains center specific and highly operator dependent. Additionally, some cases of "renal artery stenosis" are actually due to stenosis of proximal iliac vessels due to severe peripheral vascular inflow limitations and may be missed by ultrasound. The role of magnetic resonance imaging (MRI), while promising, is still not defined. Once diagnosed, percutaneous angioplasty is generally successful although surgery may be necessary in some cases.

Treatment of post-transplant hypertension requires examination of the inciting factors. Dietary sodium restriction, less than 150 mEq/day, is essential and should be the initial approach. Despite the salt dependent nature of post-transplant hypertension, diuretics should be used cautiously as volume depletion may exacerbate cyclosporine and tacrolimus toxicity leading to renal dysfunction. While a uniform regimen of anti-hypertensive medications has not been adopted, calcium channel blockers (CCBs) are generally recognized as the agents of choice in CNI treated patients. CCBs preferentially dilate the afferent arteriole and thus may reduce vasoconstriction and the renal insufficiency caused by CNIs. Dihydropyridine CCBs, such as nifedipine, isradipine and amlodipine do not significantly interfere with cyclosporine metabolism, while nicardipine and nondihydropyridine CCBs, such as verapamil and diltiazem, may cause substantial elevations in cyclosporine levels (Table 1). For this reason, we typically initiate therapy with a dihydropyridine CCB. Other agents, including centrally acting alpha agonists (clonidine), beta blockers, and vasodilators including minoxidil are other useful alternatives.

Angiotensin converting enzyme inhibitors, ACE inhibitors, and angiotensin II receptor blockers, ARBs, may be extremely potent and must be used cautiously in the post-transplant setting. Because vascular disease is typically present in renal allografts (whether reversible due to cyclosporine/tacrolimus or irreversible due to CAN or renal artery stenosis) ACE inhibitors and ARBs have the potential of significantly diminishing GFR. If these agents are used, starting with the lowest possible dose is advisable with frequent monitoring of the serum creatinine and potassium.

DIABETES MELLITUS

Diabetes mellitus is a common problem following even successful renal transplantation due to an increasing prevalence of diabetic patients receiving kidney transplants as well as the development of post-transplant diabetes. While previously referred to as post-transplant diabetes mellitus (PTDM), the preferred term currently is new-onset diabetes mellitus after transplant (NODAT). The presence of diabetes confers an increased risk of vascular complications, infections, premature death as well as higher rates of renal allograft loss. The overall incidence of NODAT has varied depending on the definition used, immunosuppressive regimen and patient population. Generally accepted risk factors include increasing age, family history of diabetes, impaired glucose tolerance pretransplant and Black and Hispanic race. Hepatitis C and polycystic kidney disease are now recognized as contributing factors to NODAT.

Immunosuppressive therapy undoubtedly plays a significant role in the development of NODM. Glucocorticoids cause insulin resistance and a dose dependent effect on glucose metabolism can be seen. In a study of steroid withdrawal, there was a reversal of NODAT in 10 percent of patients in the withdrawal arm compared to controls. Unfortunately, one quarter of the patients initially withdrawn from steroids eventually resumed therapy due to acute rejection. Cyclosporine may be diabetogenic by increasing insulin resistance but may also decrease insulin secretion. Tacrolimus is generally viewed as more diabetogenic than cyclosporine, although this effect is also dose dependent. Decreased insulin secretion with destruction of pancreatic beta cells is the primary mechanism involved. Mycophenolate mofetil does not appear to affect glucose metabolism. Rapamycin has not been extensively studied but may have conflicting effects on glucose metabolism.

Treatment for diabetes has improved with the understanding of the pathophysiology of this process and risk factors in renal transplant recipients. Weight loss remains the cornerstone of therapy and cannot be overemphasized as this will improve insulin resistance. Bariatric surgery has resulted in resolution of diabetes that may be independent of weight loss and associated with the gastrointestinal neuroendocrine system. Newer anti-diabetogenic agents, especially the thiazolidinediones (such as pioglitazone) may improve insulin production and utilization. In stable patients, modification of immunosuppressive agents may be considered, realizing that withdrawal of immunosuppressive agents even in long-term patients may result in acute rejection. Insulin is recommended if diet control does not affect hyperglycemia (2-hour postprandial glucose level of <200 mg/dL or <11.1 mmol/L).

POST-TRANSPLANT BONE LOSS

Post-transplant bone loss following renal transplantation is a type of renal osteodystrophy that combines the effects of preexisting bone disease, from dialysis and chronic renal failure, with bone loss due to renal transplantation. This post-transplant bone loss is frequently referred to as osteoporosis although it may not have the same pathophysiology as osteoporosis found in the general population. Nevertheless, osteoporosis still is the cause of a significant number of fractures. In addition to osteoporosis, avascular necrosis is a significant debilitating skeletal complication afflicting up to 15 percent of renal transplant recipients receiving glucocorticoids. In this disorder, death of the marrow cells and associated trabeculae and osteophytes occur. These two disorders result in joint replacements, and are a major cause of expense and morbidity following organ transplantation.

Bone loss following renal transplantation occurs frequently and occurs early. In patients receiving maintenance steroids, most studies have demonstrated uniformly a rapid bone loss of 5 to 7 percent within the first six months after transplantation. This rapid rate of bone loss slows considerably after the 6 to 12 months and thereafter proceeds at a loss of approximately 1 percent per year. This bone loss results in significant fractures with cross-sectional studies reporting a prevalence rate of 5 to 11 percent in nondiabetics and up to 45 percent in insulin-dependent diabetics.

The cause for this significant bone loss is indeed multifactorial, including pre-transplant factors, the post-transplant environment and immunosuppression. Pre-transplant factors include long-standing chronic renal failure, metabolic acidosis, diuretics, hyperparathyroidism and aluminum bone disease. In the post-transplant period, much focus has rightly been placed on immunosuppressive agents, specifically glucocorticoids. Glucocorticoids act directly on osteoblasts to decrease collagen synthesis and also accelerate bone resorption by inducing a secondary hyperparathyroid state. These effects are dose dependent and partially explain the high rate of bone loss early post-transplant. However, prednisone dosages even as low as 7.5 mg/day can cause bone loss and alternate day prednisone regimens have not halted bone loss. In addition to glucocorticoids, the CNIs, cyclosporine and tacrolimus also have a deleterious effect on the bone. These agents cause increased osteoclastic activity leading to high turnover bone loss. Post-transplant factors other than immunosuppressive agents include chronic allograft dysfunction, either newly induced or failure to resolve secondary hyperparathyroidism and gonadal dysfunction. The major risk factor for avascular necrosis is the use of glucocorticoids, however a cumulative dosage has not consistently been shown to be causative. Regardless, once radiographic changes occur, reducing the glucocorticoid dose or changing to alternate day regimens are ineffective to retard the pathologic process.

The diagnosis of post-transplant bone loss is most commonly assessed with the use of Dual Energy X-ray Absorptiometry (DEXA) bone densitometry. Although other techniques exist, assessment of lumbar spine and the dominant hip is the preferred method. The WHO has classified bone density according to the T score expressed as standard deviations from a control population matched for age and race in a young person, as opposed to an age-matched control (Z score). Osteopenia defined as a T score from -1 to -2.5 and osteoporosis as $\geq$-2.5. Baseline determinations for assessment of preexisting bone mass followed by periodic evaluations every one to two years is recommended. MRI is the preferred diagnostic test to diagnose avascular necrosis.

Treatment of post-transplant bone loss must take into account the multifactorial nature of this process. The cornerstone of therapy involves adequate calcium intake between 1000 to 1500 mg/d in addition to supplemental vitamin D therapy. Due to subtle declines of renal function and indolent secondary hyperparathyroidism, measurement of intact PTH and vitamin D levels should be obtained and therapy with 1,25 Vitamin D administered. Correction of metabolic acidosis and endocrinologic (including gonadal status) abnormalities, minimizing drugs responsible for bone loss in addition to a weight bearing exercise program are critical adjuncts. Treatment with bisphosphonates has shown success in preventing bone loss in glucocorticoid treated patients as well as transplant patients. Oral bisphosphonates such as alendronate and risidronate can cause gastrointestinal irritation and severe esophagitis. They should be used cautiously in patients with impaired renal function, creatinine clearance less than 30 cc/min, as well as in women of child bearing potential due to their long duration of effect on developing bone.

INFECTIOUS COMPLICATIONS

Infectious complications following renal transplantation remain an important cause of morbidity but fortunately are now a much less frequent cause of mortality due to better post-transplant management, anti-viral therapy and fewer episodes of acute rejection requiring potent immunosuppression. However, the correct diagnosis of infections in renal allograft recipients, using a systematic and logical approach, will avoid an expensive and time consuming workup as well as reduce morbidity. A high index of suspicion is required in the evaluation of immunosuppressed patients as they may not manifest a fever and leukocytosis which may be explained by the use of glucocorticoids.

One of the most useful approaches in the evaluation of any infection in a transplant patient is to determine the elapsed time from the date of the transplant. It is useful to consider three distinct time periods:

1. First month post-transplant - Infections in this period are generally related to the surgical procedure and hospitalization. As such, most infections and organisms encountered are the same that nonimmunosuppressed patients would contract. Wound infections, urinary tract infections, indwelling intravenous line infections or pneumonia are common while opportunistic infections are unusual. Antibiotic therapy should thus be directed toward typical causative organisms.

   Urinary tract infections early post-transplant are associated with a high incidence of bacteremia, pyelonephritis and a high rate of relapse when treated with a conventional course of antibiotics. Initial intravenous antibiotics followed by a prolonged course of appropriate oral antibiotics are appropriate during this time.

2 One to six months post-transplant - Opportunistic infections predominate in this time period. Cytomegalovirus (CMV) is the most important cause of infections during this period and alone, may account for two thirds of the febrile episodes. CMV is complex and has long been a cause of significant morbidity and mortality until anti-viral therapy became available. The CMV cannot only cause CMV disease, but is associated with atherosclerosis and can itself cause further immunosuppression allowing the manifestation of more severe infections such as *Aspergillus fumigatus, Listeria monocytogenes* and *Pneumocystis carinii.* With the advent of valgancyclovir, prolonged courses of viral prophylaxis is now commonly used for three to six months.

   Most adult transplant patients have previously been exposed to CMV. This group of patients may experience symptoms within the first few months post-transplant. Patients at increased risk include those treated for acute rejection, especially with anti-T cell therapy (OKT3 or anti-thymocyte globulin). Symptoms include fever, often with rigors and in a daily relapsing pattern, leukopenia and elevated liver transaminases and less commonly gastrointestinal ulcers (gastric or colonic) or pneumonia. An exceptionally high risk group includes recipients who are CMV negative receiving an organ from a CMV positive donor. These patients should receive CMV prophylaxis at the time of transplantation with recent studies demonstrating a significant reduction of CMV disease with 200 days of prophylactic treatment.

   Diagnosis, while often suspected on clinical grounds, is typically confirmed by demonstration of viremia using polymerase chain reaction (PCR). Treatment generally consists of either intravenous ganciclovir or oral valganciclovir for 14 to 21 days depending on the severity of the infection. An oral formulation of ganciclovir is available but has limited bioavailability. Valganciclovir, an oral prodrug of ganciclovir, has much greater bioavailability and is the preferred oral agent.

3. Longer than six months post-transplant - During this period patients can be stratified into those with well functioning allografts being treated with low dose maintenance immunosuppression (approximately 75 percent of patients), and those with either advanced allograft dysfunction or those receiving large doses of potent immunosuppression due to rejection episodes. Patients with well functioning grafts develop infections typically seen in the general population, i.e. uncomplicated UTIs, pneumococcal pneumonia, influenza, etc. However, the latter group is at high risk for serious opportunistic infections such as *Cryptococcus neoformans, Nocardia asteroides, Listeria monocytogenes* and *Pneumocystis carinii.* Viral induced malignancies, such as squamous cell carcinomas or lymphoproliferative disorders (discussed below) are frequently seen in this period.

Viral hepatitis (both hepatitis B and C) have an important impact on patient outcome. Patients infected with hepatitis B experience high rates of chronic liver disease and fulminant hepatic failure in addition to hepatocellular carcinoma post-transplant. Treatment with lamivudine is effective but has a high rate of drug resistant mutant strains if used as monotherapy. Avoidance of azathioprine, mycophenolate mofetil, anti-lymphocyte preparations and reduced corticosteroids dosages may reduce viral replication and improve outcomes. In patients infected with hepatitis C, the post-transplant course may be more mild early than those infected with hepatitis B. However, fulminant hepatic failure even in those recipients who were hepatitis C negative at the time of transplant is well documented. Treatment with interferon is often ineffective and has been associated with precipitation of acute rejection. Combination therapy with interferon alfa and ribavirin has greater efficacy but may result in significant anemia from hemolysis and is often avoided in those patients with compromised renal function. Given this, most centers tend to avoid transplanting young, uninfected recipients with hepatitis C positive donor organs due to the nearly universal reinfection that occurs. Although controversial and a diminishing practice, older patients, those with a more limited life span as well as those already infected with hepatitis C may be more appropriate candidates for receiving a hepatitis C positive kidney given the generally long duration required for clinical liver disease to manifest.

POLYOMAVIRUS

One area of renal transplantation that has received significant attention recently has been graft failure caused by polyomavirus. Although reports of polyomavirus were noted as early as 1971, it has only recently been recognized as an important cause of renal dysfunction and ultimately organ failure.

Polyomavirus is a nonenveloped, double stranded DNA virus that has 70 percent homology with simian virus 40. Two polyomaviruses have been described, JC and BK, named after the initials of the original patients. The JC virus has been linked as the cause of progressive multifocal leukoencephalopathy. The BK virus has affinity for the urogenital tract, thus it is the BK virus that has been associated with renal dysfunction postrenal transplant.

Primary infection with the BK virus typically occurs in childhood by the oral or respiratory route and does not cause specific symptoms. As with many viral infections, most adults have been exposed and infected with more than 80 percent prevalence on serologic testing. After infection, the virus remains dormant in the urogenital tract. Immunocompetent individuals occasionally shed virus in the urine, however, it is the immunosuppressed patients that are at increased risk for viral reactivation. Although high tacrolimus levels are a risk for development of BK nephropathy, this condition has also been associated less commonly with cyclosporine usage. There is limited evidence that sirolimus is associated with a reduced risk for BK nephropathy.

BK infections have consistently been found as a cause of hemorrhagic cystitis in bone marrow transplant patients, ureteral stenosis following renal transplantation and as a cause of interstitial nephritis in kidney (but not other solid organ) transplant recipients. After remaining latent in the urogenital tract, viral activation occurs in up to 60 percent of renal-transplant recipients with shedding of the urothelial cells. Although frequently asymptomatic and of no clinical consequence, it is this shedding of the urothelium that forms a rational basis for diagnosis of the more serious BK nephropathy.

The key to diagnosis of BK nephropathy is a high index of suspicion in a patient with unexplained graft function deterioration. Unfortunately, the virally infected cells in the renal interstitium and tubules incite a mononuclear infiltrate that mimics acute rejection. A rationale basis for the diagnosis of BK nephropathy lies in the detection of sloughed inclusion bearing cells of the urothelium. These so called "decoy cells" can be easily detected in Papanicolaou stained urine sediment. Although not highly specific for actual BK nephropathy infection, the sensitivity of decoy cells is extremely high (reported up to 100 percent) and in their absence, BK nephropathy is unlikely to be present. If decoy cells are detected in the face of graft dysfunction, renal biopsy should be performed to evaluate for BK infection. Even experienced nephropathologists may have difficulty distinguishing BK nephropathy from acute rejection. Therefore, use of immunohistochemical staining or in situ hybridization has been useful. The use of PCR for the detection of BK virus DNA in the plasma as an alternative to renal biopsy has been reported. If BK DNA is not detected, it has been reported that the negative predictive value is 100 percent with a100 percent sensitivity. However, this highly sensitive technique has also detected BK DNA in up to 23 percent of normal subjects, therefore tight standards and controls are needed with this method. In addition to these techniques, prospective screening protocols are now being employed using highly sensitive plasma PCR to detect low-grade viral replication to allow earlier intervention.

Once the diagnosis of BK nephropathy has been established, treatment is aimed at preventing further viral replication. In the past, graft failure has been reported in nearly 70 percent of patients. This exceedingly high rate of graft loss may, in part, be explained by the confusion of this disease with acute rejection, the resultant heightened immunosuppression leading to further viral injury, and an ongoing reluctance of transplants professionals to markedly curtail immunosuppressive therapy. Currently, the cornerstone of treatment for biopsy proven BK nephropathy is intensive reduction of immunosuppression. With this strategy, virally induced tubulointerstitial injury can remit and renal function can stabilize. In addition to enhancing innate immunity, anti-viral therapy is frequently necessary. Unfortunately, no specific anti-viral therapy is yet available. Cidofovir has been reported to be efficacious; however, it must be used cautiously in renal failure and now is currently rarely used. Leflunomide is more efficacious and well tolerated and has become the preferred agent in treating BK infections, in conjunction with immunoreduction. In the future, refined screening methods to allow early diagnosis and treatment will almost assuredly improve the once dismal prognosis for this condition.

POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDERS

One of the most devastating complications following renal transplantation is the development of a post-transplant lymphoproliferative disorder, commonly referred to as PTLD. The PTLDs are actually a heterogenous group of malignancies with a varied presentation and etiology. Although PTLDs are relatively uncommon following renal transplantation, occurring in only 1 to 2 percent of renal allograft recipients, as a group they are a common cause of malignancy and constitute 21 percent of tumors excluding nonmelanoma skin cancers and *in situ* carcinoma of the uterine cervix. The mortality rate on average is 40 to 50 percent but can be as high as 100 percent in cases of intracranial PTLD. Given the importance of these disorders, a basic understanding of the pathogenesis, diagnosis and treatment among physicians caring for renal transplant recipients is paramount.

The pathogenesis of PTLD has centered around the Epstein-Barr virus (EBV) which is now established as having a critical role in tumor development. In solid organ transplant recipients, the majority of PTLD cases arise from the recipient's B lymphocytes. In virtually all cases, EBV genome is detectable in the transformed B cells. Given these findings, the current schema for development of PTLD is that EBV is transmitted to either a seronegative EBV transplant recipient or under intense immunosuppression, the EBV infects the B lymphocyte and undergoes viral replication. This ultimately results in B cell transformation and activation culminating in unregulated proliferation.

Consistent with the pathogenesis of PTLD, risk factors for acquisition include EBV status and overall immunosuppression. Patients seronegative for EBV at the time of transplant are at especially increased risk, particularly those patients developing a primary infection in the setting of anti-lymphocyte preparations. Several studies have reported an incidence of PTLD of 23 percent (in the seronegative patients) versus approximately 1 percent in seropositive recipients. Not only is the overall "total body burden" of immunosuppression important, but the specific agent used. With the introduction of newer and more potent immunosuppressive agents, PTLD has occurred more frequently and earlier compared to dual therapy with azathioprine. The introduction of cyclosprine has hastened the development of PTLD from 48 months with azathioprine to 15 months in cyclosporine treated patients. Anti-lymphocyte preparations such as OKT3 further accelerate tumor development to seven months according to studies by Penn. Studies looking at the cumulative dose of OKT3 in cardiac transplantation suggest that a total dose greater than 75 mg was associated with a nearly six-fold higher incidence of tumor development with a mean interval to diagnosis of only 1.5 months after transplantation. Tacrolimus, even more so than cyclosporine, has resulted in dramatically high rates of PTLD in children undergoing liver transplantation. Thus, risk factors placing recipients at high risk for PTLD include EBV positivity, seroconversion in the setting of multiple courses of anti-lymphocyte preparation (such as OKT3), with a baseline immunosuppressive regimen consisting of tacrolimus.

The diagnosis of PTLD requires tissue biopsy. Critical features to help distinguish a true PTLD as opposed to an inflammatory disorder include: (1) demonstration of EBV infection of many of the cells, (2) presence of monoclonal or oligoclonal cell populations using cellular markers, (3) disruption of the underlying architecture by a lymphoproliferative process.

Treatment of PTLD is controversial and until recently did not have a uniform approach in part due to lack of understanding of the pathogenesis as well as lack of randomized, controlled trials. Traditionally, chemotherapy had been used to treat PTLD along the lines of nontransplant related nonHodgkin's lymphoma. It has become clear that immunoreduction should be the first line of therapy once the diagnosis of PTLD is made. In select populations, immunoreduction alone results in a nearly 90 percent remission of PTLD. Depending on the extent and clonality of the tumor, discontinuation of azathioprine/mycophenolate mofetil and a 25 to 50 percent reduction of cyclosporine/tacrolimus are reasonable initial interventions. Systemic anti-viral agents such as acyclovir or ganciclovir may be beneficial due to their ability to inhibit lytic, replicating EBV. However, these agents are less effective in latent or oncogenic EBV. Chemotherapy is generally reserved for patients with life-threatening disease or progressive disease despite initial therapy. Rituximab, a monoclonal antibody against B lymphocytes, anti-CD 20, has shown considerable promise in combating this disorder, usually in combination with traditional chemotherapeutic agents.

KEY POINTS

1. Kidney transplantation has made tremendous advancements in a relatively short time.
2. One-year graft survival has increased over the years.
3. Although acute rejection rate has decreased, incidence of CAN has increased.
4. Numerous immunosuppressive drugs are in the market and more are to come.
5. Therefore, choice of immunosuppressive combination should be safe and minimize a variety of infectious and neoplastic complications that cause death despite functioning graft.

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SECTION 8

PEDIATRIC POPULATION

✦ Management of Urinary Tract Infection in Pediatrics

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Management of Urinary Tract Infection in Pediatrics

Udai K Kala

INTRODUCTION

The incidence of urinary tract infections (UTI) in infancy and childhood is approximately 2 to 8 percent with a mean of 5 percent. The impact of these UTI is to identify and treat any underlying risk factors especially in the first 10 years of life to prevent further renal damage and renal failure as renal replacement therapy is extremely expensive. It is not only important to the patient and the family but also the health budget of the country!

The diagnosis of UTI is based on a high index of suspicion, as the manifestations are varied and nonspecific. Therefore the diagnosis is highly dependent on screening urine. The macroscopic urine is observed for clarity and dipstick for leukocytes, blood and nitrites; microscopy for leukocytes and bacteria and confirmed by culture of appropriately collected specimen of urine.

Definition

Demonstration of growth of 10^5 colonies of a single organism per ml. of clean voided urine specimen on three separate specimens, any number of bacteria cultured from a suprapubic aspirate and 10^{3-5} colonies on a catheter specimen, the probability of a UTI is 95 to 99 percent.

Low colony counts despite clinically significant UTI (Block, et al.) may be caused by:

1. High volume urine flow
2. Recent antimicrobial therapy
3. Fastidious and slow growing organisms, e.g. enterococci
4. Low urine pH (<5) and specific gravity (<1.003)
5. Bacteriostatic agents in the urine
6. Complete obstruction of a ureter
7. Use of inappropriate culture techniques
8. Chronic indolent infections

CLASSIFICATION OF URINARY TRACT INFECTION

The classification is anatomical, i.e., depending on the site of infection.

a. Lower tract cystitis or cystourethritis and or
b. Upper tract involvement, i.e., pyelonephritis.

Clinically, UTI may be symptomatic or asymptomatic and complicated or not.

Method of Urine Collection

This is the single most important basis for the diagnosis of UTI as inappropriate specimen lends itself to painful, unnecessary and costly investigations of the patients.

1. Suprapubic aspiration
2. Midstream clean catch
3. Catheterization—not for routine use, but necessary to obtain urine specimen in a suspected UTI when antibiotics need to be commenced expediently.
4. Bag specimens for screening purposes only, i.e. cannot send such a specimen to the laboratory for culture due to contamination.

Bladder is an abdominal organ in the first two years of life and easily amenable to suprapubic aspiration. It is the ideal method of collection of urine in infancy and patients with palpable bladders for the unequivocal diagnosis of UTI. Technically, aspiration can be performed safely and painlessly by applying topical and local anesthesia before aspiration of the bladder percutaneously but it is not practical. Clinically a full bladder is indicated by suprapubic dullness on percussion but if facilities allow, one can confirm a full bladder by ultrasound on site to obtain a suprapubic specimen.

Midstream clean catch urine (MSU) must be collected with the labia or prepuce retracted and cleaned with water or saline as the antiseptics may inhibit the growth of bacteria. Catheterization should not be used routinely as it may cause infection if there is no infection. But it may be an important tool to obtain urine in a septic infant who needs antibiotics urgently.

Bag specimens are extremely useful for screening purposes but accurate diagnosis of UTI and subsequent radiological investigations cannot be based on that type of specimen due to contamination of the specimen from the close proximity of the anus. It cannot be stressed sufficiently that the appropriate specimen should be collected for culture.

Storage of Urine

Urine should be stored at 0 to 4°C until it is plated. If the specimen is older than 20 to 30 minutes at the maximum 3 hours in colder environments when plated then contamination takes place and any growth under those circumstances is questionable. Therefore an office technique such as the urine dipslide plating is an important tool in the primary health care centers.

Parameters secondary to infection in urine are the following:

1. Nitrites
2. Leukocyte esterase
3. Pyuria
4. Increased C-reactive protein in serum for pyelonephritis and in urine for a UTI.
5. Raised urinary glycoaminoglycans

A negative nitrite test does not exclude a UTI, as the urine needs to be in the bladder for at least three to four hours for conversion of the nitrate to nitrite by the Gram negative organisms. This factor is of importance in infants and children that have not gained continence as they empty their bladder reflexly every two to three hours, resulting in a false negative nitrite test.

Leukocyturia is defined as >4000 wcc/ml of urine of 5 white cells per high power field in centrifuged urine and 10 white cells per high power field unspun urine.

Leukocyturia is not diagnostic of UTI. There are many other causes of leukocyturia, such as:

1. Fever
2. Dehydration
3. Vulvovaginitis
4. Balanitis
5. Viral infections
6. Oral polio vaccination
7. Bilharzia
8. Tuberculosis of the kidney
9. Appendicitis
10. Membranous glomerulonephritis

UTI can occur without leukocyturia especially in recurrent infections.

Hematuria occurs frequently in children with symptomatic UTI and is macroscopic in 5 to 20 percent of those with acute cystitis. However, determination of hematuria or albuminuria is of no value in establishing diagnosis of UTI.

Leukocyte esterase alone has a mean sensitivity of 83 percent and specificity of 78 percent compared to a positive nitrite test with a mean sensitivity of 53 percent and specificity of 98 percent but both combined has 93 percent and 72 percent mean sensitivity and specificity, respectively.

PATHOGENESIS

Depends on host susceptibility and the virulence of the organism. Mechanisms of renal damage by infection are reviewed by Jahnukainen, et al.

Factors contributing to host susceptibility:

1. Age; especially under one year prone to scarring when pyrexial.
2. Sex; females (except in the neonatal period) due to shorter urethra and uncircumcised males in the neonatal and first year of life.
3. Anatomical abnormalities, for example obstruction by posterior urethral valves.
4. Functional abnormalities, for example vesicoureteric reflux (VUR) and voiding disorders.
5. Malnutrition especially in kwashiorkor which is multifactorial, for example, Vitamin A deficiency

causing transitional epithelium changing to squamous and also decreased mucin production thus the organism has a better grip via fimbrae and adhesins and also not trapped due to lack of mucin. Poor perineal toilet and associated gastroenteritis causing an ascending UTI. Possible lack of secretory immunoglobulin A (IgA) thus compromising local immunity.

6. Immune deficiency or compromise or underlying systemic disease and in acquired immune deficiency syndrome (AIDS), it seems more related to the poor nutritional status than immune deficiency state.
7. Low secretory IgA.

Virulence of the organisms depends on:

1. K_1 capsule especially with *Klebsiella* and *E.coli* infections, which interfere with opsonization and phagocytosis due to poor immunogens and activators of complement cascade.
2. "P" fimbrae, which adhere to uroepithelium despite washout effect of bladder due to urination and can cause parenchymal renal infection despite the absence of VUR.
3. X-binding adhesins, functionally heterogeneous but defined as resistant to both D-mannose and alpha-D-Gal and beta -D-Gal.
4. Type 1 common pili that agglutinate guinea pig erythrocytes are inhibited by D-Mannose.
5. O-Serotypes that produce toxins such as hemolysin or Colcin V and elaborate adhesins.
6. Aerobactin production, which is an iron binding hydroxamate that is required by *E.coli* for aerobic metabolism and multiplication.

Generally uropathogenic *E.coli* strains tend to possess multiple virulence properties and these factors are important in colonization and infection of children with anatomically normal genitourinary tracts.

Pathogens

The most common urinary pathogens are:

1. *Escherichia coli*
2. *Proteus mirabilis*
3. *Klebsiella*
4. *Pseudomonas*
5. *Citrobacter*
6. *Serratia*
7. *Streptococcus fecalis*
8. Fungi-*Candida albicans*

Aerobic Gram-negative rods are responsible for most UTI's. E.coli is the most common of these organisms, causes 75 to 90 percent of acute infections and 70 to 80 percent of recurrent infection in the overall pediatric population. In the first three months of life the spread is mainly hematogenous, whereas six months onwards an ascending infection is common. Fungal and unusual bacterial infections occur in immune compromised patients, obstructive uropathy, e.g. posterior urethral valves and instrumentation of the urinary tract, e.g. cystoscopy.

CLINICAL FEATURES OF URINARY TRACT INFECTION

These are age-dependent and often nonspecific. Diagnosis is dependent on a high index of suspicion and screening of urine.

Clinical features in the different age groups are presented in Table 1.

Important factors on history of bladder and bowel function which predispose to UTI are:

1. Voiding frequency
2. Urgency
3. Squatting or other holding maneuvers
4. Day wetting
5. Poor or fractionated stream
6. Prolonged voiding

Table 1. Clinical features of urinary tract infections in the different age groups

	Neonate	*Infant*	*Older Child*
Incidence	0.5–2%	4%	4.4%
Sex	Males 84% Mainly uncircumcised	Males > Females	Females >>Males (F: M-3:1-8:1)
Route	Hematogenous	Ascending mainly Some septicemia	Ascending Symptomatic or Asymptomatic
Signs	Septicemia Irritability Lethargy Convulsions Hypotonia Hypothermia Diarrhea Feeding difficulty Jaundice	Fever Failure to thrive Chronic diarrhea Persistent Vomiting Low grade fever Constipation Abdominal pain Malodorous urine Dribbling urine	Fever Suprapubic pain Frequency Urgency Dysuria Enuresis Change in pattern of voiding

7. Straining during voiding
8. Constipation, soiling

On physical examination important points to note are:

1. Fever
2. Hypo or hypertension
3. Growth failure
4. Abdominal examination for masses especially renal and urogenital abnormalities
5. Rectal examination for; thickened bladder wall, bladder stones and ureteroceles.

MANAGEMENT OF URINARY TRACT INFECTION

General Measures

1. Increased fluid requirements up to one and half times normal due to loss of concentrating ability, pyrexia increasing insensible losses and to utilize the 'washout' effect of urine flow to flush out the organisms.
2. Antipyretics and analgesics, e.g., paracetamol, which has reasonably wide margin of safety.
3. Avoid nonsteroidal anti-inflammatories, e.g., mefenamic acid causing interstitial nephritis especially in the face of possible dehydration and an inability to concentrate urine.
4. Alkalinization of urine except with Proteus infection.
5. Double voiding.
6. Perineal toilet.
7. Avoid bubble bath which may cause chemical urethritis.
8. Correcting constipation is one of the most important aspects of management.

Patients with complicated infections require hospitalization, parenteral antibiotics and evaluation for presence of significant structural abnormalities. If patients are reliable, management can be successful in febrile young children with daily parenteral antibiotic therapy from a day treatment center allowing close medical supervision and facilitating investigations related to UTI.

Patients with uncomplicated infection can be managed on an outpatient basis with emphasis on documenting resolution of their bacteriuria then elective evaluation for potential anatomic or functional abnormalities of urinary tract.

SUMMARY

Complicated UTI is defined as high fever, clinically ill or "toxic" appearance, persistent vomiting and moderate to severe dehydration .

Uncomplicated UTI includes fever but not necessarily toxic look, able to take fluids orally and mild dehydration only.

If fever does not settle after two to three days of therapy, suspect:

a. Resistant bacteria
b. Obstruction to urine flow, e.g., valves, stones, etc.

Evidence of urinary obstruction includes distended bladder, mass in the loin, hypertension, increased urea and creatinine and electrolyte disturbances and acidosis.

Specific Treatment

Appropriate antibiotics are recommended for 10 to 14 days. Shorter courses of antibiotics are not recommended to treat children as they have a higher recurrence rate. The latest studies show that there is no significant difference in the efficiency between completing treatment with an oral third generation cephalosporin which was started with intravenous therapy for the first 3 days compared to 14 days of intravenous therapy only.

Neonates

The usual choice is ampicillin and gentamicin or cefotaxime parenterally (IVI) due to a bacteremia/ septicemia. Gentamicin peak and trough levels need to be monitored and dosage adjusted accordingly.

Ampicillin 75 to 200 mg/kg/day (IVI) for 10 to 14 days
Tobramycin 5 mg/kg/day (IVI) for 7 to 10 days
Gentamicin 5 mg/kg/day (IVI) for 7 to 10 days
Amoxicillin 40 mg/kg/day (IVI) in 3 divided doses for 10 to 14 days

Antibacterial Agents for Oral Treatment of Urinary Tract Infection

These are indicated generally for uncomplicated lower urinary tract infections and for step down therapy after a minimum of three days parenteral therapy for complicated or and acute pyelonephritis. Choose one of the following:

Sulfisoxazole 120 to 150 mg/kg (p/o), divided q 4 to 6 hour for 10 to 14 days.

Cotrimoxazole 6 to 12 mg/kg (p/o)TMP 30 to 60 mg/kg SMX divided q 12 hours not in the first 2 months of life for 10 to 14 days.

Amoxicillin 20 to 40 mg/kg (p/o) divided q 8 hours for 10 to 14 days.

First, second and third generation oral (p/o) cephalosporins:

Cephalexin 50 to 100 mg/kg (p/o) divided q 6 hours for 10 to 14 days.

Cefuroxime 100 to 150 mg/kg (p/o) divided q 8 hours for 10 to 14 days.

Cefixime 8 mg/kg (p/o) divided q 12 hours for 10 to 14 days.

Cefpodoxime 10 mg/kg (p/o) divided q 12 hours for 10 to 14 days.

Loracarbef 15 to 30 mg/kg (p/o) divided q 12 hours for 10 to 14 days.

For inpatient management of complicated UTI, choose one of the following administered intravenously (IVI):

Cefotaxime 150 mg/kg IVI every 6 to 8 hours for 10 to 14 days.

Ceftriaxone 75 mg/kg IVI every 12 to 24 hours for 10 to 14 days.

Ceftazidime 150 mg/kg IVI every 6 to 8 hours for 10 to 14 days.

All these can cause gallbladder sludging, aggravating neonatal jaundice.

If severe or resistant organisms, use appropriate aminoglycoside in correct dosage depending on renal function and peak and trough blood level:

Tobramycin 5 mg/kg/day as single intravenous infusion for 7 to 10 days-nephrotoxicity with trough >2 μg/ml and cochlear ototoxicity.

Gentamicin 5 mg/kg/day as single intravenous infusion for 7 to 10 days-nephrotoxicity with trough >2 μg/ml and irreversible vestibular ototoxicity with sustained peak >12 μg/ml.

Amikacin 15 mg/kg/day as a single intravenous infusion for 7 to 10 days-nephrotoxicity with trough >10 μg/ml and cochlear ototoxicity.

Re-culture urine 48 to 72 hours of antibiotics to ensure infection is cleared and check again 4 weeks later for relapse or recurrence.

Prophylaxis

Prophylactic antibiotic therapy following a UTI has become controversial and presently there are trials underway to determine its necessity. Use one of the following:

Trimethoprim (alone) 2 to 4 mg/kg (p/o) single dose at night if continent or twice daily otherwise.

Cotrimoxazole 2 to 4 mg/kg (p/o) single or twice daily.

Nitrofurantoin 2 mg/kg (p/o) single or twice daily dependent on normal renal function. Not in the first two years of life due to propensity for fibrosis of the lung.

To give prophylaxis until appropriate investigations in children with recurrent infections, VUR or obstructive uropathies (stasis) are completed. Nitrofurantoin is recommended as the first choice prophylaxis treatment with recurrent UTI and urinary tract abnormalities despite increased gastrointestinal side effects.

Radiological Investigation

All investigations are dependent on local expertise and availability of different imaging modalities. Some of the imaging recommendations are not evidenced based. Of utmost importance is the diagnosis of UTI on appropriately collected specimen of urine. Radiological investigations should be done as recommended, in all boys and girls especially when a luxury of prenatal sonar is not available, older girls with recurrent symptomatic bacteriuria not investigated previously and any patient with evidence of diminished renal function, hypertension or persistent hematuria and or proteinuria.

Abdominal Plain Film

A plain film may hint towards a specific disease complex, e.g. by showing spinal dysraphism for example spina bifida, calcifications or bowel dilatation and stool retention.

Renal Ultrasound

Performed on all patients but is operator and apparatus dependent. It is safe, noninvasive and no special preparation is required. Good indication of renal size, shape, dilation of pelvicalyceal system, bladder wall thickness, anatomy of distal ureters and urethra.

Doppler imaging is useful to demonstrate areas of decreased perfusion in children with focal or diffuse areas of pyelonephritis. Ultrasonography is excellent in detecting:

1. Congenital abnormalities - horse-shoe kidney, agenesis, etc.
2. Space occupying lesions - cystic kidney, neoplasms
3. Urinary stasis - hydronephrosis
4. Urolithiasis

Ultrasonography is unreliable in detecting VUR, renal scarring or inflammatory change and on its own may be inadequate for investigating UTI in children for those reasons.

Intravenous Pyelography (IVP)

Not indicated initially unless there is need to detect upper tract abnormalities or scarring. It is a good investigation for medullary sponge kidney, infantile polycystic kidney disease.

Voiding Cystourethrography (VCU)

VCU is recommended for detection of:

1. VUR
2. Posterior urethral valves
3. Ureterocele
4. Bladder diverticulae, stones, etc.

VCU can be done soon after the infection is cleared. When obstructive uropathy is suspected, e.g., posterior urethral valves then it should be done as soon as the urine is sterile. Children with symptoms suggestive of UTI following VCU should be treated for *Pseudomonas aeruginosa* pending culture results.

Radioisotope Studies

This is more of a tool for follow up studies. It is not utilized as a first line investigation in unless indicated for other reasons. Renal static and dynamic isotope studies allow a semi-quantitative assessment of renal parenchymal disease, renal function and urinary drainage.

DMSA (Tc 99 labelled Dimercaptosuccinic acid) scans in the acute phase is done to differentiate renal parenchymal infection (pyelonephritis) from that of the lower urinary tract. A scan three to six months later will diagnose scar formation in the kidney.

The pitfalls of isotope studies are the poor anatomical resolution, the lack of urethral visualization, the restricted grading capability and the limitations in low grade or transient VUR.

Obstruction of the urinary tract accounts for an important subgroup of patients with renal disease because nephron loss can be prevented or minimized by early diagnosis and treatment.

Most anatomic obstructions would be detected by radiological investigations but the functional disorders would require a cystometrography (CMG), which can be performed at the earliest at the age of five years.

Summary of anatomical and functional obstruction follows in Table 2.

Children with detrusor instability who use various posturing maneuvers to avoid urinary incontinence have a significantly higher incidence of UTI than those who do not attempt to obstruct urine flow. Clinically constipation, is most commonly associated with detrusor instability.

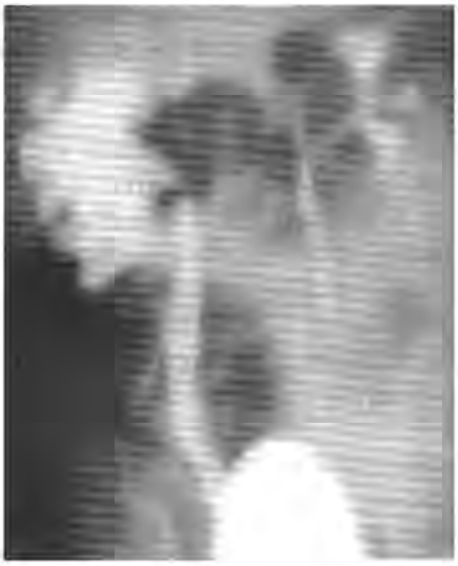

Figure 1: Grade 5 right vesicoureteric reflux and grade 4 left vesicoureteric reflux

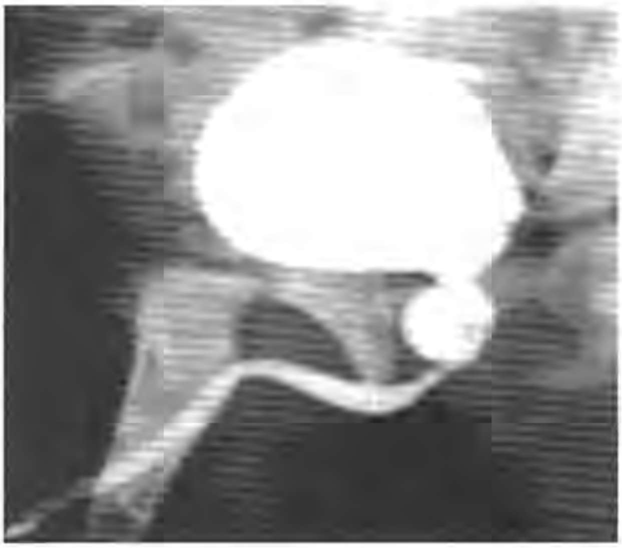

Figure 2: Typical posterior urethral valves (PUV) with dilated prostatic urethra and trabeculated bladder

Vesicoureteric Reflux

The primary defect is possibly due to reduced length of the ureter in the submucosa of the trigone of the bladder. The defect is congenital and not associated with underlying neuromuscular obstructive phenomenon. Children with their first UTI, who are under one year, have a higher incidence of VUR than patients over one year of age; 40 percent and 25 percent, respectively. The defect resolves spontaneously with growing age in 80 percent of patients.

There is a significant association between elimination problems (constipation 23 percent, bladder instability 19 percent, infrequent voiding 16 percent and primary VUR.

VUR is graded according to the International Study group:

- 1 and 2 of slight importance.
- 3 to 5 gross reflux with or without dilation of collecting system with risk of renal damage in the face of infection.

VUR is found in 20 to 50 percent of patients with UTI in most European and American studies.

Black Americans and Africans show significantly lower prevalence of reflux. There is a familial occurrence as high as 30 to 40 percent of siblings (asymptomatic) of the index case of UTI being investigated. Therefore, it is important to screen siblings of the index case to prevent future renal impairment.

20 percent of school age girls with asymptomatic bacteriuria may have VUR.

Renal scarring may be preventable if the infection is detected and treated promptly but permanent renal damage in children with acute pyelonephritis may occur especially in the presence of VUR, recurrent UTI and older age.

Only severe reflux with dilation and with medically uncontrollable infections will require surgical intervention in the form of ureteral reimplantation. In the majority, antimicrobial prophylaxis and attention to prevention of constipation will tide them over until spontaneous resolution of reflux occurs. The newer less invasive techniques which involve endoscopic periureteric injections of polydimethylsiloxane (Macroplastique), dextranomer/hyaluronic acid copolymer (Deflux) or glutaraldehyde cross-linked bovine collagen have been assessed and in a recent Cochrane collaboration. The current treatment options include surgery involving re-implantation of ureter(s), which is either successful or not, with no option of repeat surgery if unsuccessful. Surgery plus long-term antibiotics, long-term antibiotics alone and endoscopic correction using different materials were compared and the results were that surgery decreased the number of feverish UTI but did not change the number of children developing any UTI or kidney damage. Day admission and endoscopic correction seem cheaper and the materials are more bio-friendly and the option to repeat the procedures until reflux stop is possible.

Table 2. Summary of anatomical and functional obstruction

Anatomical 3–21%	*Functional*
Posterior urethral valves	Detrusor instability
Pelviureteric junction obstruction	Urethral hyperactivity
Ureterocele	Infrequent voiding
Ureterovesical junction obstruction	Neurogenic bladder
Stones	Constipation

Follow Up

Relapse or recurrence is common - 30 percent after first UTI and 60 to 65 percent after second and third UTI. Recurrence is more common in girls. Some experts have recommended that periodic surveillance of urine culture for up to a year should be done after an initial UTI. However, the value of treatment of asymptomatic bacteriuria is unproven. Rather child and parents should receive advice about recurrent infection and if symptoms of acute UTI develop to seek medical attention.

KEY POINTS

1. The initial task is to establish the diagnosis of a UTI. The clinical setting, method of specimen collection, bacterial colonies count and infecting organism are all-important considerations. Next, the infection is classified as complicated or uncomplicated.
2. Complicated infections require hospitalization and parenteral antibiotics initially and can be stepped down to oral agents after infection is under control.
3. Appropriate imaging studies are imperative. All children with well-documented UTI deserve diagnostic evaluation. To prevent further infection and damage to the kidneys which will depend on the expertise and equipment of the institution.

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Textbook of
NEPHROLOGY

Diabetes has constituted a large part of nephrology practice. Diabetes-related renal disease including end-stage renal disease makes up the considerable volume of patients in nephrology offices throughout the world. Therefore, the editor feels deeply that including several chapters on diabetes will educate the readers with comprehensive knowledge of the pathophysiology of diabetes in this text unlike other textbooks on the subject of nephrology. The pathophysiology such as what does high glucose do to body function is written on the platform of fundamental research in the editor's laboratories. The more we know about the fundamentals of diabetes, the safer the care we will be able to provide to our patients. In other words, it is the editor's conviction that physicians should pay utmost attention to enabling a productive and healthy life for our diabetes patients rather than dictating a therapy which leads to dialysis and the burden it imposes on the patient and the family.

The chapter on logical management of diabetes should help the readers to accomplish this defined task. The focus of this third edition of the book is a conservative nephrology practice directed toward healthy living, clear of artificial means of prolonging life.

Anil K Mandal is a native of India and a naturalized citizen of the Unites States. He graduated from Calcutta National Medical College and is a Diplomate of the American Board of Internal Medicine and in Nephrology (Kidney Disease and Hypertension). He is the author of many books and articles on research in diabetes and kidney disease. He is a two-time Fulbright Scholar to India and Visiting Professor to 24 countries where he has lectured on diabetes, high blood pressure, and kidney disease.

He began the Mandal Diabetes Research Foundation for the prevention and treatment of diabetes based on his knowledge that diabetes is the most common cause of kidney failure worldwide.

His convictions are that—in the office, patients come first and, in the home, children come first. He is dedicated to helping diabetic patients live a good life and not enter dialysis.

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